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Editorial

Body Density, Fat, and Fat-Free Weight

In recent years the development of methods to assess the gross composition of the human body, particularly to discriminate between fat and fat-free fractions *in vivo* by means of densitometry, has attracted considerable interest in biology and medicine [*1*]. Progress in this field, however, has been hindered to a great extent by poorly defined concepts and by non-discriminatory usage of formulas. It is the present purpose to (1) review critically the methodology used and the principles involved in determining body density and fat content, (2) clarify the meanings and limitations of these measurements, and (3) explore the potential usefulness of these determinations.

Body Density Measurement. By definition, density (D) is mass (M) per unit volume (V). Accordingly, body density (D_b) is body weight in air (M_a) divided by body volume (V_b):

$$D_b = \frac{M_a}{V_b} \qquad (1)$$

Although body weight in air is easily determined, accurate estimation of body volume requires considerable technical skill. At present, two methods are used for measuring body volume. One is based on the well known principle of Archimedes, the other on the dilution principle. In the former, body volume is obtained as the difference between the weight in air and the true weight in water (M_w):

$$V_b = (M_a - M_w)/D_w \qquad (2)$$

where D_w is the density of water at bath temperature. It is realized that the true weight in water is composed of at least two components, i.e., the apparent weight under water (M'_w) and the weight of water displaced by the residual air in the lungs and airways (V_r):

$$M_w = M'_w + D_w \cdot V_r \qquad (3)$$

From the relationships expressed in equations 1, 2 and 3, one acquires a formula which specifies four measurements required to obtain body density:

$$D_b = M_a \cdot D_w/[M_a - (M'_w + D_w \cdot V_r)] \qquad (4)$$

These are (1) body weight in air (M_a), (2) water density at bath temperature (D_w), (3) apparent weight under water (M'_w), and (4) the residual air in the respiratory system (V_r) [*1*]. There is a small amount of gas also in the digestive tract but in practice this may be neglected because gas volume in this system averages an insignificant 115 ml. or less in normal subjects [*2*].

In the second method, which is based on the dilution principle, a test subject is placed in an air-tight chamber of known capacity, a measured amount of indicator gas is injected and mixed uniformly in the chamber. Then a gas sample is withdrawn and analyzed for its concentration. This technic demands a highly sensitive and reliable device for determining the concentrations of indicator gas [*3*].

Duplicate measurements on thirty-four normal subjects within six months by the dilution technic showed an average difference in density values between the first and second runs of 0.0006 gm. per ml. [*3*], whereas repeated measurements in our laboratory of five normal

subjects within two weeks by the hydrostatic weighing method yielded a mean difference in density of 0.0028 gm. per ml. In view of the much greater sources of error inherent in assumptions made in the estimation of fat, as will be shown later, a reproducibility of density measurement within 0.005 gm. per ml. is acceptable [4].

Derivation of Fat Content. The two body constituents which influence body density greatly are (1) fat, which is the lightest component of body tissue, and (2) minerals, which are the heaviest. Several attempts have been made in the past to obtain a quantitative relationship between fat content and body density. The basic principles involved in these endeavors are (1) that the sum of the fractions of the body mass is equal to unity and (2) that the total body volume is equal to the sum of the volumes of the components. If we divide the body into two components, for example, fat (f)* and fat-free tissue (ff), the sum of these two fractions must be equal to 1.0 according to the first principle:

$$1 = f + ff \tag{5}$$

while the second principle may be expressed as follows:

$$\frac{1}{D} = \frac{f}{D_f} + \frac{ff}{D_{ff}} \tag{6}$$

where D, D_f and D_{ff} are the densities of whole body, fat, and fat-free tissue, respectively. From equations 5 and 6 the following formula is attainable; it indicates that when the densities of fat-free and fat components are known, fat content may be estimated from the body density alone:

$$f = \left(\frac{D_{ff}}{D} - 1\right) \Big/ \left(\frac{D_{ff}}{D_f} - 1\right) \tag{7}$$

The density value for human fat given by Fidanza et al. [5] is 0.9000 gm. per ml. with no significant difference according to sex or bodily location. However, adequate data on the density of the fat-free component of the human body are not available at present and presumably will not be available until the fractional differences in each of the major constituents of fat-free mass, namely, water, protein and minerals, are determinable quantitatively in health as well as in pathologic conditions. Conversely, it is not yet proved that the fat-free component is of uniform, fixed composition among subjects with various degrees of skeletal development and hydration.

Physiologically, the closest approximation to the density of the fat-free component is that of the leanest body, and the reported value is approximately 1.097 gm. per ml. [1]. Since even the leanest person must possess a certain amount of essential lipids which are widely distributed in nervous system and in cellular matter, the density of the fat-free body must exceed the value of 1.097 gm. per ml. The first attempt to estimate human fat content from body density was made by Rathbun and Pace [6] in 1945. They assigned to the densities of fat-free and fat components 1.097 gm. per ml. (specific gravity 1.1 at 25°C.) and 0.917 gm. per ml. (specific gravity 0.919 at 15°C.), respectively. As already mentioned, the density value for the fat-free component is conjectural at best, and the density value for fat, that is 0.917 gm. per ml., is no longer valid. Above all, what is more important, the substitution of these values in equation 7 implicitly presupposes a fixed composition of reference body structure, either in the sense of fat-free body or "lean body mass." This assumption has never been verified in man and cannot be used without reservations.

In 1953 Keys and Brožek [7] published a classic paper in which they set forth a method of estimating fat content from body density. Because of the possible fallacy embodied in applying the density value of fat-free component in equation 7, they determined (1) the density of the "standard body" of twenty-five healthy men on the average twenty-five years old and (2) the density of "obesity tissue" gained by experimental overeating. By applying these two density values, which were 1.0629 gm. per ml. and 0.9478 gm. per ml., respectively, to equation 7, it was possible to obtain an equation for the fraction of "gained" or "obesity tissue." Since the primary components of "obesity tissue" are (1) fat, (2) cellular matter, and (3) extracellular water, they determined directly the fraction of extracellular water by the thiocyanate method and indirectly estimated the fraction of cellular matter from older studies. Thus the composition of "obesity tissue" was calculated to be 62 per cent fat, 24 per cent cellular matter and 14 per cent extracellular water. Using these data and making a further assumption of 14 per cent of fat in the "standard body" they were

* "Fat" is used strictly in the chemical sense.

able to obtain equation 8 for fat content from body density:

$$f = \frac{4.201}{D} - 3.813 \qquad (8)$$

On the basis of logical clarity and minimal yet reasonable assumptions made in the derivation, the formula by Keys and Brožek appears to be the most reliable one at present when data on body density alone are available. It is necessary, however, to mention the limitations of this formula in practical application. As implied in the process of derivation, this equation is valid only over a relatively normal nutritional range; that is, in weight gains up to the point where fat is of the order of 25 per cent of body weight, or in weight losses down to the point where fat approaches 10 per cent of body weight.

An outstanding contribution in this field was made in 1956 by Siri [8] who presented one of the clearest expositions of estimating fat content. The basic principles upon which his derivations are founded are identical with those used by previous workers, such as Rathbun, Pace, Keys and Brožek, except that the fat-free component is further divided into body water (w) and non-fat solid (s) components:

$$1 = f + w + s \quad (1 = f + w + s) \qquad (9)$$

$$\frac{1}{D} = \frac{f}{D_f} + \frac{W}{D_w} + \frac{S}{D_S} \qquad (10)$$

where D_w and D_S are the densities of water and non-fat solid, respectively. From these relationships, equation 11 is obtained:

$$f = \frac{D_f}{D_S - D_f}\left[\frac{D_S}{D} - w\left(\frac{D_S - D_w}{D_w}\right) - 1\right] \qquad (11)$$

This formula specifies that when the densities of fat, non-fat solid and water are known, fat content may be estimated from body density and total body water. Since the density values for water and fat are known, the density value of non-fat solid remains to be established. Siri reasons that the two major constituents of non-fat solid are protein and minerals and that since the highest ratio of minerals to protein in lean persons is approximately 0.5, the combined density of these substances is 1.640. However, the ratio of minerals to protein decreases to one-third in an obese person, reducing the combined density to 1.560. Thus he gives the median value of 1.600 for the density of non-fat solid. Therefore, by substituting the density values for water (0.9933), fat (0.9000) and non-fat solid (1.600) in equation 11, the following formula is derived for the estimation of fat content from body density and total body water:

$$f = \frac{2.057}{D} - 0.786w - 1.286 \qquad (12)$$

The salient features in this formula are (1) it does not require a fixed composition of basic body structure, such as fat-free body, "lean body mass" or "standard body," (2) its range of application is much wider than the formula of Keys and Brožek because it is completely independent of the state of hydration, and (3) it may be perfected further to allow for individual variation in the composition of non-fat solids when more accurate estimates of minerals and protein can be made *in vivo* [9,10].

In our laboratory the original Behnke technic [1] was used after some modifications had been made: the total lung capacity of the test subject was determined by the N_2 dilution technic in the course of routine pulmonary function tests several days before or after the hydrostatic weighing. Prior to the weighing the vital capacity was measured and its two-third level was marked. The subject exhaled into the spirometer to this mark just before immersion into water. Thus the amount of air in the respiratory system during hydrostatic weighing was the difference between the total lung capacity and the exhaled amount of air registered on the spirometer. In this fashion the measurement was repeated three times in each subject. The mean difference between the minimum and maximum body density values of these triple determinations in thirty-seven healthy male subjects was 0.0033 gm. per ml., which indicated good reproducibility of this procedure.

In addition to the determination of body density, the total body water was estimated by a tritiated water dilution technic [11] in sixty-five normal male subjects. Having both values of body density and total body water, it was possible to calculate fat content by means of both equations 8 and 12. In Figure 1 the values for fat content estimated by equation 12 (Siri's formula) are plotted on the ordinate, while that by equation 8 (Keys and Brožek's formula), on the abscissa. The diagonal line is the hypothetical relationship between two determinations when they are in perfect agreement. It is apparent from this diagram that equation 12 yields consistently higher values for fat content

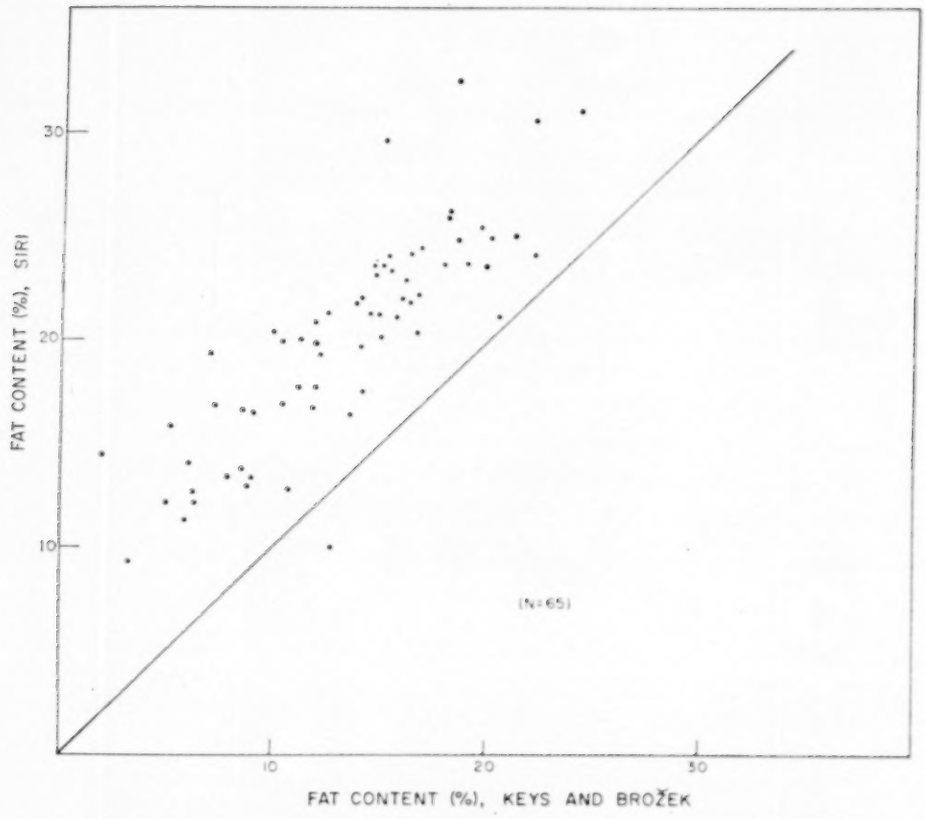

FIG. 1. Fat content as estimated by equations 8 and 12. (See text for details.)

than does equation 8, the mean difference being approximately 6 to 7 per cent.

Recently Siri [*4*] made a mathematical analysis of the uncertainty of the various methods for estimating fat due to biological variability and experimental error. He claims that when the body density alone is used, assuming a precision of ± 0.0025 gm. per ml. in the density measurement, the standard deviation of the estimate of fat is within ± 4 per cent of gross body weight, while the inclusion of total body water with a precision of ± 2 per cent, as in equation 12, reduces the over-all uncertainty in the estimation of fat to a standard deviation of ± 2 per cent of gross body weight. The discrepancy between values of fat based upon the same density measurements using the derivation of Keys and Brožek and of Siri (Fig. 1) is obviously greater than can be attributed to experimental error alone; it must be due to a systematic difference between assumptions made for the "standard man" of the former and the reference body of the latter. Whereas the combined use of density and body water no doubt increases the precision of the estimate of fat by reducing random errors, the true values cannot be stated with certainty at the present time.

Normal Values of Body Density and Fat Content. Even bearing in mind the limitations previously outlined, the estimation of gross body composition by densitometry provides valuable information on the effects of growth and aging, of diet and activity in healthy subjects and in various pathologic conditions. Data on body density in infants and early childhood are not available at present but excellent data over the age range of twenty to fifty-five years in normal men and women are reported by Brožek and his coworkers [*12,13*] and are schematically shown in Figure 2. In this diagram age is plotted on the abscissa and body density and fat content* on the ordinate. The upper unbroken line indicates the body density of males, the lower unbroken line that of females. Notice that there is an unmistakable trend of progressive reduction in body density in both sexes as age progresses. The broken lines indicate the fat content, the lower broken line representing the fat content of males, the upper broken line that of females. At

* Estimated, using equation 8.

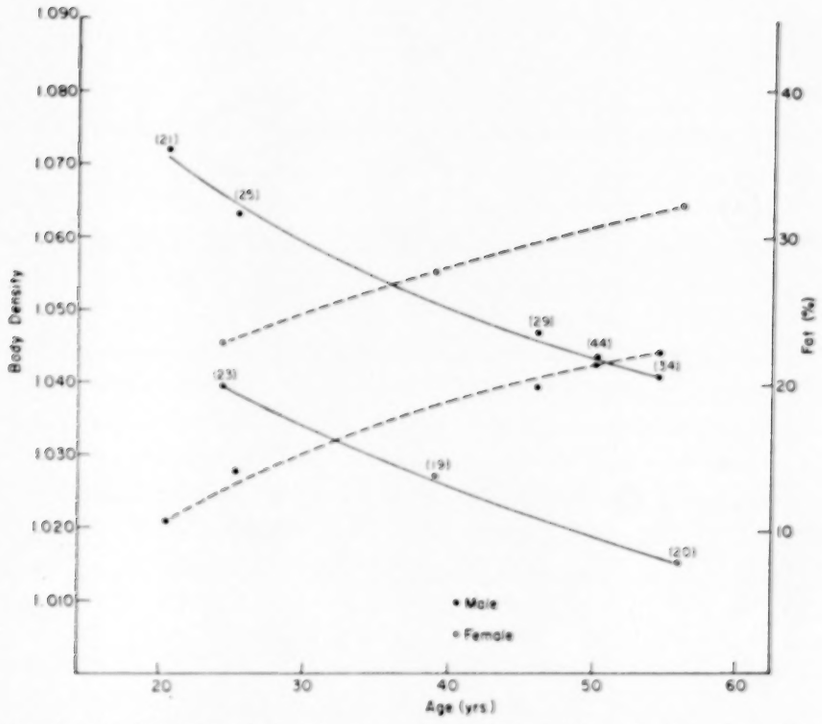

FIG. 2. Body density and fat content as a function of age (from the data of Brožek and his co-workers [*12,13*]).

the age of twenty, the average fat content of the male is about 10 per cent of body weight and it climbs to 23 per cent at the age of fifty-five. The fat content of the female at the age of twenty is already 23 per cent and it reaches 32 per cent at the age of fifty-five. The figures in the parentheses represent the number of subjects tested in each age group. It should be noted that the body weights of the test subjects are between 95 to 100 per cent of standard, hence the test subjects were neither overweight nor underweight.

Applications in Physiology and Medicine. The dichotomy of the human body into fat and fat-free components *in vivo* enables us to re-examine some of the basic physiologic parameters, such as basal metabolic rate and cardiac output, on the basis of a newly-acquired reference; namely, fat-free weight. To date the basal metabolic rate has been expressed as a function of gross body weight or surface area. The relevance of employing gross body weight as a criterion of the metabolic activity may be questioned since gross body weight includes a variable quantity of fat, which ranges from 10 to 35 per cent in healthy men and women. Likewise, the unsubstantiated theories underlying use of the body surface area for this purpose have been a source of constant dispute in the history of medical physiology. Thus a further attempt to evaluate the usefulness of the new standard reference (i.e., fat-free weight) in relation to basal metabolic rate is justified. Should fat-free weight represent the metabolically active tissue mass because it is the tissue mass devoid of metabolically less active fat component, then it may be postulated that the basal metabolic rate is best predictable from fat-free weight rather than from either gross body weight or surface area.

The data of von Döbeln [*14*] have been analyzed to test the validity of this hypothesis. He determined basal metabolic rate and body density by the hydrostatic weighing technic in seventy healthy men and women whose ages ranged from twenty to forty years. In Table IA, the basal metabolic rate is examined in relation to three physical references of gross body weight, surface area* and fat-free weight. The total correlation coefficients are all highly significant at less than a 1 per cent level, and these coefficients are not statistically different from each other according to the test of Fisher's Z transformation [*16*]. Additional information regarding the relative value of these references in

* Estimated from the Sendroy's nomogram [*15*].

TABLE 1
CORRELATION AND REGRESSION ANALYSES

	Y(ml./min.)	X_1(kg.)	X_2(M^2)	X_3(kg.)	
A. Gross Body Weight (X_1), Surface Area (X_2), Fat-Free Weight (X_3) and Basal Metabolic Rate (Y) in Seventy Healthy Men and Women					
Total correlation (r)		$r_{y1} = 0.65$	$r_{y2} = 0.70$	$r_{y3} = 0.80$	
Multiple correlation (R)					$R_{y.123} = 0.82$ $S_{y.123} = 18.6$
Partial correlation		$r_{y1.23} = -0.33$	$r_{y2.13} = 0.32$	$r_{y3.12} = 0.56$	
Standard partial regression (b′)		$b'_{y1.23} = -0.92$	$b'_{y2.13} = 0.94$	$b'_{y3.12} = 0.77$	
B. Gross Body Weight (X_1), Surface Area (X_2), Fat-Free Weight (X_3) and Basal Cardiac Output (Y) in Twenty Normal Subjects					
Total correlation (r)		$r_{y1} = 0.46$	$r_{y2} = 0.53$	$r_{y3} = 0.72$	
Multiple correlation (R)					$R_{y.123} = 0.87$ $S_{y.123} = 0.49$
Partial correlation		$r_{y1.23} = -0.33$	$r_{y2.13} = 0.08$	$r_{y3.12} = 0.75$	
Standard partial regression (b′)		$b'_{y1.23} = -1.51$	$b'_{y2.13} = 0.34$	$b'_{y3.12} = 1.78$	

predicting the basal metabolic rate is thus obtained by the analyses of the multiple and partial correlations, as well as by Snedecor's "standard partial regression" [*16*]. The results of these analyses indicate that the multiple prediction is better than prediction based on any single variable, that the independent effect of fat-free weight accounts for the greatest proportion of variance, and that the quantitative superiority of fat-free weight over surface area is not very great as reflected in the "standard partial regression coefficient."

A similar analysis of the relationship between basal cardiac output and three physical references was made utilizing the data by Taylor et al. [*17*]. They determined basal cardiac output and body density by the hydrostatic weighing method in twenty healthy male subjects whose ages ranged from nineteen to thirty-one years.* The result, shown in Figure 3 and Table 1B, indicates again statistically significant correlations of all three references with basal cardiac output, but the relative value of these references is in the order fat-free weight, gross body weight, surface area. The Fisher's Z test shows no significant difference between the coefficients of total correlation.

On the basis of the foregoing analyses it may be concluded that fat-free weight is the best single predictive variable for either basal metabolic rate or cardiac output. Needless to say, however, analyses of other basic physiologic parameters, such as maximal oxygen uptake, blood volume, glomerular filtration rate, creatinine excretion and total body potassium, in relation to fat-free weight, surface area and gross body weight have to be made to ascertain the validity of these standards of reference. At this stage of investigation it is our opinion that fat-free weight is an important standard of reference and re-examination of basic physiologic variables on this basis may furnish us a clearer insight into the dynamic processes of normal as well as abnormal functions of the human body.

In regard to applications to clinical medicine, the quantitative subdivision of the whole body

* The data on fourteen subjects are not included in this analysis because in these subjects residual air was not measured, but instead a constant value (1.5 L.) was assumed. Such a practice introduces a greater error in the estimation of fat-free weight. For the same reason, the data by Miller and Blyth [*18*] were not used in the analysis of the basal metabolic rate.

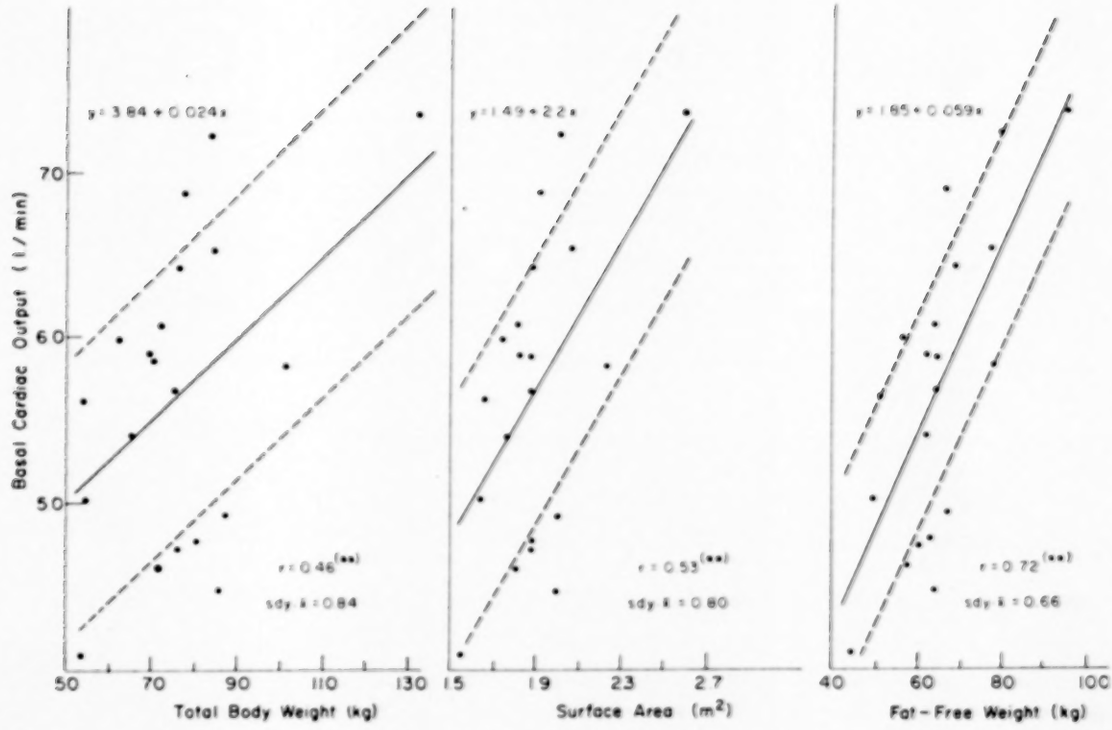

FIG. 3. Basal cardiac output in relation to total body weight, surface area and fat-free weight (from the data of Taylor et al. [17]).

into fat and fat-free weight provides a useful tool in understanding pathologic processes. To mention a few examples: (1) nitrogen and oxygen are approximately five times more soluble in fat than in water, implying that men devoid of excessive fat have a better chance of resisting decompression sickness during deep sea diving or high altitude flight; (2) it is estimated that the adipose tissue of an experimental animal takes up from six to ten times as much thiopental as other parts of the body. In accord with this finding it has been demonstrated that the duration of thiopental anesthesia is more than doubled in the lean animal as compared with the fat animal administered the same dose [19]. The administration of some anesthetics as well as therapeutic reagents which have a marked affinity for fat should be re-evaluated on the basis of fat and fat-free weight; (3) patients with muscle wasting diseases (namely, progressive muscular dystrophy and poliomyelitis) increase their fat content sometimes up to 40 per cent or more of body weight as they lose muscle and mobility. These changes are not always evident from inspection of the patient, or measuring their total body weight, or computing their surface area [20]; (4) in extremely ill patients who are undergoing severe stress due to acute injury, surgical trauma or thermal burns, the oxidation of fat proceeds at a faster rate than in simple starvation. In addition, there is a loss of nitrogen and potassium, indicating a simultaneous loss of fat-free mass. It is estimated that acute loss of body weight under severe stress at a rate of 1 kg. per day includes about 500 calories from the fat-free mass and 5,000 calories from fat [21]. Since such major changes in body constituents accompany drastic alterations in caloric requirements, and also involve a considerable change in the quantity and composition of body fluids, it is obvious that quantitative data on body composition would be of aid in the effective treatment of such patients.

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Clinical Studies

Abnormal Resting Blood Lactate*

I. The Significance of Hyperlactatemia in Hospitalized Patients

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DURING a period of years several patients have been found to have severe acidosis; this occurred spontaneously during hospital admissions for other reasons and culminated in the death of the patients. The blood of these subjects showed very marked accumulations of lactate ion, sufficient, as lactic acid, to account for a severe acidosis. They had no signs to indicate the presence of other known causes of acidosis. In addition to these, a number of other patients with greater or lesser lactatemia have been observed in widely varying clinical states. Therefore, it seemed of some interest to determine, insofar as possible from their records, the clinical significance of the finding of a high resting blood lactate in such patients. The present communication analyzes the clinical outcome in thirty-seven patients with abnormal lactatemia occurring at rest with various other associated findings.

METHODS

The data were obtained in hospitalized patients, principally at the Massachusetts Memorial Hospitals, between 1953 and 1960. Arterial or venous blood samples were analyzed for lactate and pyruvate as previously described [*1*]; blood O_2 and total CO_2 determinations were carried out by the manometric method of Van Slyke [*2*]. Hydrogen ion concentrations were determined with the glass electrode at 37.5°C. and bicarbonate and P_{CO_2} calculated by the Henderson equation.

RESULTS

Normal Values. Blood lactate concentrations are very variable, and measurements obtained in patients at random probably reflect many clinically insignificant influences. Control data necessary for examining this point are given in Figure 1. The figure illustrates values for normal resting blood lactate obtained in this laboratory during a six year interval, taken during periods near to the times when patient's with lactatemia were studied. Of these various data, column II represents the most reproducible "normal" values, namely, those obtained from arterial blood collected by the most rigorous technic [*1*] from fasting normal subjects resting in the laboratory in a nearly basal state (mean 0.620, σ = 0.077 mM/L.). By contrast, the normal values obtained by more practical technics are also illustrated in Figure 1; from these it can be seen that the analysis of venous blood collected in ordinary syringes from unprepared subjects on a hospital ward leads to more variable results which are, on the average, higher (mean = 0.997, σ = 0.12 mM/L.). In individual instances such a random procedure may give a very much higher blood lactate level.

In Figure 2 (column I) a second series is illustrated. These subjects were hospitalized, but recently recovered from minor infections; data obtained were from a different ward at a different time, but they show a close similarity to column IV of Figure 1 (mean = 1.04, σ = 0.13 mM/L.). Figure 2 (column II) also illustrates the blood lactates found in ninety-six patients at rest who were considered seriously ill and had a variety of different diseases. It seems clear from column II that no significant elevations of blood lactate were present in this group (mean = 1.119, σ = 0.14 mM/L.). The patients

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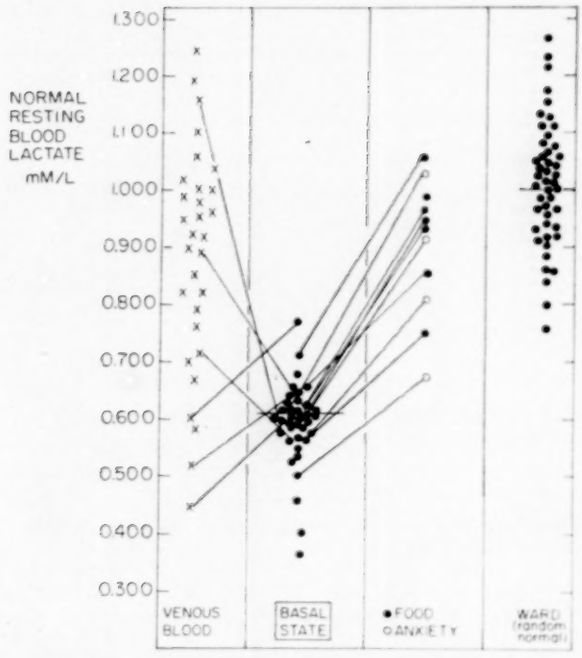

FIG. 1. Scatter diagrams of "normal" blood lactate concentrations. Each point is the mean of several values from samples drawn in succession from one patient. Column II shows arterial blood (drawn with instantaneous denaturation) from fasting, basal subjects. Columns I and III show values derived from venous blood in basal subjects, or from arterial blood one hour after a meal or during overt anxiety; the lines connect values obtained in the same subject. In column IV venous blood samples collected on the ward from unselected patients recovered from minor complaints are shown.

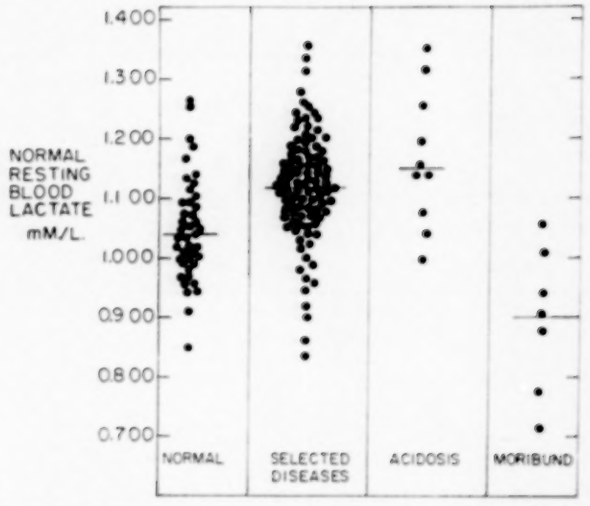

FIG. 2. Blood lactate concentrations in diseased subjects. Column I shows normal patients who have recovered from minor illnesses (a separate series from column IV, Fig. 1). In column II values observed in patients with a variety of disabling diseases as enumerated in the text are shown. In column III are shown patients with acidosis (arterial blood pH 7.12 to 7.28) due either to renal failure and uremia or to diabetes, prior to any treatment. Column IV shows moribund patients who subsequently died within one hour of the sampling of blood.

had the following disorders: sixteen were disabled with acute infections (including severe paralytic poliomyelitis, spinal and bulbar); seven with chronic pulmonary disease (with or without cyanosis); five with severe anemias of various causes; seven with heart disease (myocardial infarction, congestive failure and cyanotic congenital defects); eight with cerebrovascular accidents with or without coma; five with hepatic disease (including severe jaundice with hepatitis or decompensated cirrhosis); eight with renal disease with and without uremia, several with endocrine disorders (diabetes, four, thyrotoxicosis, two and myxedema two); twelve with a variety of malignant tumors with and without metastases (including metastases to bone, liver, lung, lymph nodes and general dissemination); and a group of seventeen with miscellaneous abnormalities including anesthesia, the postoperative state, and acute intoxications with methyl alcohol, paraldehyde and ethanol. Incorporated incidentally into this group are patients in whom such influences are involved as prolonged or strict bed rest, moderate pain, fever, high and low levels of serum potassium and sodium, edema and dehydration, and administration of various drugs (including digitalis, nitroglycerin, various sedatives and narcotics, antibiotics, aspirin, ephedrine and adrenal steroids). Since no tendency toward high blood lactate was noted in association with any of these conditions, the data may be summarized as giving no clinical lead to the cause or causes of the hyperlactatemias observed in certain other patients.

Figure 2 (column III) illustrates the levels of blood lactate found in patients with acidosis of either of the more familiar types, four with diabetes (untreated) and six with renal disorders (four had terminal uremia of pyelonephritis and two acute renal shutdown, virtually anuric). The finding of nearly normal blood lactate (mean 1.15, range = 1.02 to 1.34 mM/L.) in acidosis due to other independent causes indicates the distinction of these forms of acidosis from those to be considered as "lactic acidosis" [7]; it further suggests that acidosis itself, i.e., high hydrogen ion concentration, does not cause lactate accumulation. Figure 2 (column IV) shows the result of one

further survey which seemed necessary in view of later findings, the blood lactate levels in patients in the terminal stages of disease, i.e., the effect of impending death itself. The data presented are those obtained by chance within fifteen minutes to one hour prior to death; all the patients had been severely ill for more than twenty-four hours with various diseases. The data in column IV (mean 0.901, range 0.71 to 1.05 mM/L.) indicates that significant elevations of blood lactate were not noted in the "terminal state."

All the values in Figures 1 and 2 were obtained from patients who were immobile and had been at rest for at least thirty minutes. The well known effect of physical exercise in elevating blood lactate raises the important question of how much lactatemia could be produced by unrecognized muscular contractions. Figure 3 illustrates the order of magnitude of this effect. Column II shows the "hospital normals" from Figure 1. Column III represents the peak blood lactates found in six patients instructed to contract as many body muscles as possible while holding the limbs stationary. In column IV the peak blood lactate concentrations previously found in forty supine subjects during vigorous walking movements of the legs are shown [*3*]. Both types of exercise, of course, were obvious to observers, and therefore they were probably more strenuous than any occult tension which may have been present in "resting" patients. In addition, significant elevations of blood lactate produced by these maneuvers were transient and could not be sustained for more than a few minutes.

Figure 3 (column V) summarizes the levels of blood lactates which are referred to here as "hyperlactatemia," in a scatter diagram. These values are, for the most part, of such a different order of magnitude that the sources of variation considered in columns II, III and IV of the figure are insignificant by comparison. Therefore, the causes of the variations discussed in relation to columns I to IV offer no satisfactory explanation of hyperlactatemia. Also included in column V, for completeness, is a number of lower values; all are significantly elevated for resting subjects. All the patients were fasting and resting in bed.

The basic causes of these elevated lactate levels were further investigated by examination of the accompanying changes in blood pyruvate [*4–6*]. In a general way, blood pyruvate concentrations were similarly elevated, but a more

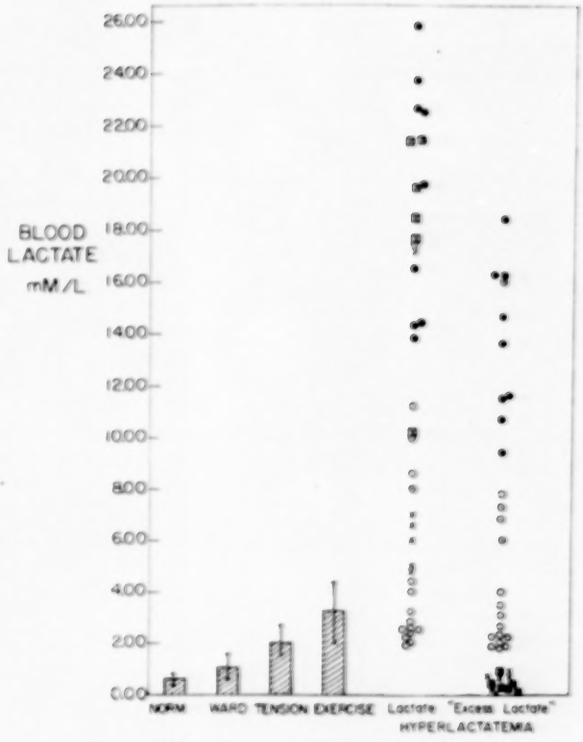

FIG. 3. Elevated blood lactate concentrations. Columns I and II show normal subjects (from column II, Fig. 1), and "ward normals" (from column I, Fig. 2). In column III the effect of voluntary contraction of all the muscles of the body while lying stationary in bed is shown. Column IV demonstrates the effect of vigorous exercise of the legs in a walking motion while lying supine in bed. In column V unexplained elevations of blood lactate found in fasting patients at complete rest are demonstrated. Crosses denote group 1 as defined by the relationship of blood lactate to pyruvate; those in boxes are the values in primary hyperventilation. Round points denote group 2; open circles are those of group 2A, closed circles 2B. Open circles with central point denote patients with circulatory failure. In column VI calculated values of "excess lactate" are shown.

exact comparison of pyruvate and lactate in individual instances is presented in Figure 3 (column VI). The points in column VI show the values of "excess lactate" [*4*] calculated from the observed lactate and pyruvate concentrations by comparison with normal values. This figure expresses the quantity of lactate accumulated in excess of pyruvate in each patient. As the figure shows, these data fall into two groups: (1) patients with little or no excess lactate, i.e., in whom body lactate had merely risen in proportion to (and probably [*4*] as a result of) the increase in pyruvate and; (2) patients with a more or less marked accumulation of excess lactate.

In view of the suggestion that excess lactate appears only if tissue hypoxia is present [*5,6*], evidences of hypoxia were sought in these patients. Anemia was not found in any patient. However, peripheral circulatory failure (reduced arterial blood pressure, tachycardia, sweating and mental confusion) was present in four, and a low arterial blood O_2 saturation in twelve. These abnormalities all occurred in group 2. No evidences of hypoxia were found in patients of group 1.

Figure 3 (columns V and VI) shows the levels of lactatemia of the patients in group 2, in whom all lactate accumulations were more than 60 per cent excess lactate, with identification of those persons in whom a cause of hypoxia was found by independent means (either hypoxemia or shock). This assumes that the "cause" which was found was in fact the basis of the metabolic hypoxia; that assumption was supported to some extent by the finding that adequate therapy was followed by restoration of the blood lactate to normal. In those with hypotension the clinical evidences of shock disappeared with blood transfusion, and blood lactates became normal within ninety minutes afterward. The remaining patients had hypoxemia, due either to acute exacerbations in chronic pulmonary emphysema or to acute bronchial asthma; it was always relieved by inhalation of 100 per cent oxygen, whereupon blood lactates fell immediately and became normal within thirty minutes, although they rose again if the breathing of oxygen was discontinued.

Therefore, Figure 3 (column VI) shows a clinical separation of group 2 into two categories: (A) those with evidences of one or another of the well-known causes of hypoxia; and (B) those with no detectable disturbance in oxygen transport in the usual sense. Group 2B also tended to show the most extreme elevations of blood lactate and hydrogen ion concentration, although this criterion was not absolute; the patients in group B usually presented primarily as having acidosis, ultimately of very severe degree. All the nine patients with lactic acidosis (group 2B) died within a few hours or days of its discovery; the more detailed characteristics of this enigmatic disease are presented separately [*7*].

COMMENTS

The reason for abnormal elevations of body lactate is not immediately obvious since no individual organ is involved which could be specifically diseased; both production and removal of lactate are active functions of every tissue of the body except the erythrocyte. Urinary excretion of this ion is usually so small by comparison with the rates of either production or absorption which occur elsewhere, that it must be considered negligible. Further data on this point will be presented at a later time, but it has become clear that absence of the kidneys would have no important influence on blood lactate. The values reported herein of patients with terminal uremia or acute renal shutdown illustrate the point better than any other evidence. Although liver and myocardial tissue commonly remove lactate from the perfusing blood during the fasting state, lactate absorption may occur, and does occur, in all tissues [*8–9*], just as net lactate production occurs in the liver under the same circumstances which bring about net production in other tissues. The normal resting blood lactate found in patients with hepatic failure is consistent with these observations. Even if one organ were found to be unable to absorb lactate in its normal fashion, this would give no explanation of the failure of the rest of the organs to do so. An organ approach to hyperlactatemia is probably too great an oversimplification to be helpful since it does not seem able to encompass the observations mentioned. The truly pertinent question is: what are the influences in these patients toward net lactate accumulation in the body as a whole, and how do they act at a cellular or molecular level, whatever tissues may be involved? At the cellular level the enzyme lactic dehydrogenase provides the only existing mechanism of both production and removal of lactate in the body; these two activities with respect to lactate, unlike those for glucose, urea or other substances, are therefore only two phases of one process. Decreased removal is identical with increased production for all the circumstances having an influence on this system which we have studied, depending merely upon what the tissue was doing beforehand. An attempt to explain hyperlactatemia assuming a real distinction, in the gross physiological sense, between production and removal would also represent an oversimplification.

Finally, it is important to consider whether or not any change in enzyme activity could explain the observed facts. This is important because the numerous and complex factors

which might affect enzyme proteins in the body may or may not have to be considered in understanding hyperlactatemia.

The level of lactate at any one time probably must be regarded as that of a steady state for the body as a whole. This would be true, strictly speaking, only when there was no net lactate production; this requirement was met, within the limits of measurement, for periods of at least thirty minutes between paired analyses in all the patients. But even when the entire illness of any patient is considered, in spite of the very high lactate levels reached, the *rate* of accumulation of lactate in the course of several days' time was "negligible." This concept is based upon two facts (1) rates of lactate production which are several hundred times as great (12 to 14 mM/L./minute) occur in human subjects within a few seconds, which is to say, at any one enzyme concentration; and (2) even these rates of change may be associated with evidence of essentially continuous equilibrium with pyruvate [*4*], or a series of steady states; this is well illustrated by the patients in group 1 reported on herein (e.g., Fig. 4). Therefore, although reaction rates are theoretically always affected by enzyme concentration, in a given situation this principle need not have any detectable effect; and, at the low rates with which we are concerned in a practical way, the two facts mentioned suggest that it does not. On the contrary, another equally well established principle does seem to be applicable here, namely that the concentration of enzyme has no effect on the steady state or equilibrium concentrations in a system. When the rate of lactate production is very small practically speaking (i.e., relative to maximal velocity), this principle is practically applicable. The inference is, therefore, that no alteration of enzyme function is suggested by the data obtained in these patients. Since lactate production is the primary difficulty, there clearly is no deficiency of enzyme activity from this point of view. On the other hand, intravenous infusions of several hundred millimoles of lactate were readily absorbed without an increase in blood concentration, and served to illustrate that the system was still readily reversible [*7*].

On this "near steady state" assumption, certain calculations have been made about the unknown concentrations of the other substances concerned in the lactic dehydrogenase system from those which are known [*4*]. If the lactate and pyruvate concentrations were known, for

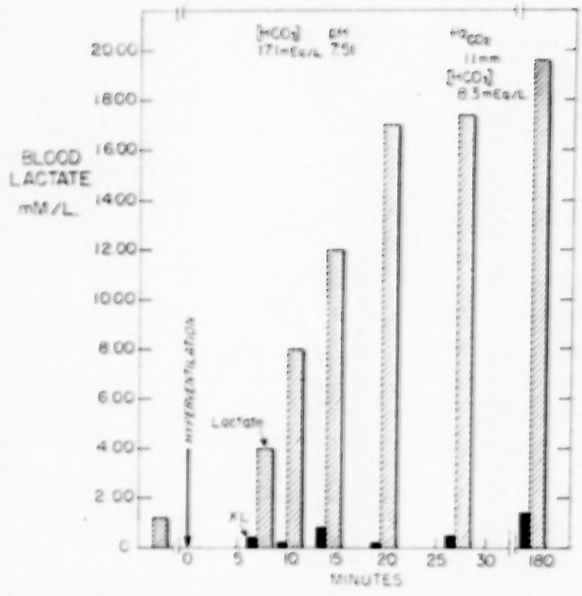

FIG. 4. Rapidly developing extreme elevation of blood lactate in a patient with primary hyperventilation (low P_{CO_2} and high pH of arterial blood) believed to be neurogenic in origin. The negligible values of excess lactate indicate the lactatemia is in group 1.

instance, the concentrations of DPN and $DPNH^+$ might be estimated; but even supposing that only changes in lactate and pyruvate are known, then changes in the state of oxidation of DPN might be estimated. From such calculations it has been suggested previously [*5*], and again in the present investigation, that "excess lactate" ($XL = [L_2\text{-}L_1] - [P_2\text{-}P_1][L_1/P_1]$) is an estimate of the energy provided by an anaerobic process for preventing increase in ($DPNH^+/DPN$) or, more exactly, energy produced as a result of a tendency of ($DPNH^+/DPN$) to increase; such an increase would reflect a relative failure of the oxidizing potential, which is normally maintained by the oxygen supply to tissues. However, when lactate increases merely in proportion to pyruvate, the same calculation gives no such evidence that oxidizing potential or supply of tissue oxygen has diminished relative to metabolic requirement. On the basis of this calculation, a tentative division of the present patients into two groups has been made. The ultimate value of such a division remains to be seen, but its success in identifying groups of patients which were ultimately recognizable clinically, especially in terms of prognosis [*7*], is notable in the present limited experience. The patients in group 1 showed no excess lactate, or less than 10 per cent of the lactate accumulation. Group 2

includes those who were found to have accumulated excess lactate in body fluids and had, in effect, very large oxygen debts which were never paid off.

Group 1. These patients did not exhibit acidosis of important degree in the proper sense of elevation of hydrogen ion concentration in body fluids. However, serum bicarbonate concentration was low in those whose lactic acid accumulation was great enough to reach the range of detection by bicarbonate estimation (4 to 5 mM/L. or more), and therefore were usually initially considered to have acidosis. Actually, six of these patients had alkalosis and had arterial blood pH's between 7.47 and 7.61 and P_{CO_2} between 16 and 24 mm. Hg. These patients had obvious pathologic hyperventilation of sudden onset; three patients had had two or more small strokes previously, while a fourth had atrial fibrillation and signs of peripheral emboli. Consequently, a primary central nervous system basis for the hyperventilation may be proposed in these patients. Two presented strongly suggestive signs of pulmonary embolism; one patient died, and the diagnosis was confirmed at autopsy. The changes in blood lactate, bicarbonate, P_{CO_2} and pH in one of these patients are shown in Figure 4. The striking effect upon blood lactate of hyperventilation and alkalosis has been reviewed previously [*4*]; the rise in lactate due to this cause is proportional to the rise in pyruvate, and no excess lactate is found. The remaining patients in group 1 had received either large doses of glucose, insulin and bicarbonate or epinephrine. Blood pH varied between 7.40 and 7.20. The effects of these procedures on blood lactate have also been described a number of times [*4*]; the effect appears to be a primary pyruvate change which inevitably raises lactate secondarily, but a detailed understanding of the causes of such pyruvate elevations does not seem possible at present and can only be recorded as an observation. All but two patients in group 1 recovered and subsequently had normal blood lactate. The prognosis in this group seems clearly to be no worse than that of the initial disease, and it is unchanged by the occurrence of lactatemia.

Group 2A. These patients had either (1) hypoxemia of recent onset and fairly severe intensity (Sa_{O_2} 62 to 84 per cent), or (2) peripheral circulatory failure due to gastrointestinal bleeding. The patients with hypoxemia, which was associated with acute bronchial asthma or exacerbations in the course of obstructive emphysema, exhibited the lowest blood lactates under consideration here. All grades of lesser lactate accumulation down to the normal range were also found in similar patients, and the examples given merely represent the higher range of elevations that may be seen; they differ only in that the lactate levels were high enough that they were repeatedly mistaken for incipient lactic acidosis (group 2B), since the lactate was largely excess lactate. Arterial hypoxemia in patients, like that of many experimental animals, even when severe, appears unlikely to be a cause of marked lactatemia. Chronic hypoxemia apparently is not a cause of lactate elevation at all. Of the ten patients in this group, six had arterial blood pH below 7.35 (7.32 to 7.22) and were therefore acidotic, but unlike the patients in group 1 Pa_{CO_2} values were elevated. As in group 1, the lactatemia in group 2A had no ominous prognostic significance; although it was caused by hypoxia in group 2A, the hypoxia in these patients was apparently due to hypoxemia and was correctible. No deaths occurred in this group.

Group 2B. The patients in this category were recognized as described in the preceding paragraphs, that is to say, by ruling out the other types of lactatemia. It has seemed very important to recognize the patients in this category because of the extraordinary course of their illness [*7*], and the ominous prognosis associated with the diagnosis. It appears that an extremely high blood lactate is most likely to indicate either this category (group 2B) or primary hyperventilation [1]; a distinction can readily be made between these two possibilities by determination of blood pH. However, if lactic acidosis is to be recognized before it reaches the extreme stage, a determination of blood pyruvate is necessary. Even when a rise in blood lactate has been identified as one due largely to excess lactate, it is not necessarily an alarming sign. The finding of low arterial blood oxygen has been (strangely) very comforting in patients with excess lactatemia, and the presence of early shock even more so. The test of oxygen inhalation may further confirm the hypoxemic cause of excess lactate accumulation. However, the apparent absence of all circulatory and respiratory abnormalities in excess lactatemia is an ominous sign; or if arterial blood oxygen is reduced, and its correction by oxygen therapy does not reduce the blood excess lactate, a serious

outcome may be anticipated. Furthermore, if acidosis is the initial finding, and lactatemia of excess lactate has already progressed to the extreme elevations illustrated in Figure 3, it would appear from the present small experience that recovery is so unlikely that any new therapeutic approach which seems reasonable ought to be tried. A more detailed description of clinical and laboratory findings in group 2B is given in the second paper of this series [7].

SUMMARY

1. When patients on a hospital ward were studied to determine the range of blood lactate concentrations to be found, the values varied from 0.430 to 26.42 mM/L.

2. A very small part of this variation was caused by the imperfect sampling technics necessary for bedside use.

3. Only a very small part of the variation could be accounted for by muscular contractions in any patient who was lying still in bed.

4. However, great elevations of blood lactate occasionally occurred in resting patients. These were encountered in a variety of clinical states which seemed to have nothing in common, and other patients with similar diseases showed no similar lactatemia in association with the disease itself.

5. The patients with hyperlactatemia had variable blood pyruvate concentrations; in some patients the elevated pyruvate level accounted for the elevated lactate, through its effects in the lactic dehydrogenase system, while in other patients there appeared to be a major accumulation of lactate in excess of this and due to some other cause. On this basis the patients were divided into groups 1 and 2.

6. Since the only other cause of a steady state of lactate accumulation is cellular hypoxia, data on circulation and respiration were collected. On this basis group 2 was further subdivided into groups A and B, the former including all patients with hypoxemia or circulatory failure.

7. All patients with hyperlactatemia except the small group 2B were found to exhibit the various known causes of lactate accumulation consistent with the accompanying changes in blood pyruvate but often only indirectly and incidentally related to the "disease" for which hospital admission was required.

8. Group 2B could not be satisfactorily explained in any clinical terms or in relation to other laboratory findings, but the group was nevertheless clinically distinct. All the patients were acidotic and all died.

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Abnormal Resting Blood Lactate*

II. Lactic Acidosis

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OVER a six-year period, a small number of patients has been observed with lactic acidosis and a syndrome of hyperpnea and dyspnea not previously recognized. Although the information available is incomplete, it is nevertheless presented because of the importance of calling attention to this condition and to the need for additional observations.

The term "lactic acidosis" refers to clinical acidosis in which the accumulated acid is almost entirely lactic acid. By this definition the term does not apply to normal persons performing hard physical exercise, since normal findings in persons who suffer no disability are easily distinguished from clinical acidosis. Acidosis means there is an accumulation of hydrogen ions and a more acid reaction of body fluids. It is not merely a displacement of extracellular bicarbonate by lactate, a finding which may be associated with alkalosis [*1*], even when hyperpnea is the major clinical characteristic. The problem presented by these patients was one of unmistakable acidosis. The definition of lactic acidosis also excludes the more common clinical acidoses which are due to diabetes or renal failure, in which the blood lactate may be coincidentally slightly elevated, since such acidoses are caused predominantly by other acids.

The previous classification of patients with hyperlactatemia into three groups [*1*] was based upon the relative changes of blood pyruvate found at the same time, because this chemical relationship successfully distinguished between different prognostic categories and also because the resulting distinctions were subject to some physiologic interpretation. The present communication gives a more detailed description of the last and uniformly fatal group (2B), those in whom lactate had accumulated far in excess of pyruvate, as is typical of hypoxia, but who presented no clinically identifiable cause for the tissue hypoxia.

METHODS

The methods employed were the same as those previously described [*1*]. In each of the present patients one or more arterial blood samples was analyzed in addition to the venous samples.

RESULTS

Clinical. The only clinical features which the nine patients had in common were (1) acidosis and (2) a fatal outcome. All were hospitalized for a period of days to weeks prior to the rather sudden appearance of an inexplicable acidosis. This period of observation is thought to exclude the possibility of ingestion of any obviously toxic chemical. A variety of common drugs had been administered during the preliminary hospitalizations; but all the drugs used have been examined for such effects in other patients [*1*], and no tendency toward acidosis or lactate accumulation was found. Diets were also normal as a result of this preliminary hospitalization, and vitamin supplements had been given. Never did two cases occur in the same hospital at the same time, and no other unusual illnesses appeared simultaneously. Table 1 lists the clinical diagnoses which caused the original hospital admissions. These diseases seem to have no common factor. Either recovery from, or definite improvement in, the original difficulties had been noted in every case before the acidosis supervened; some of the patients were considered nearly ready for discharge.

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TABLE 1

DATA ON PATIENTS WITH LACTIC ACIDOSIS

Case No. and Age	L	XL	P	L/P	$(HCO_3)_2$	Blood pH	Sa_{O_2} %	Time (hr.) and Procedures	Diagnoses and Laboratory Data
	(milliequivalents per liter)								
1,56	10.43	6.7	0.876	11.9	15.0	7.25	97	6 ...	Peptic ulcer, postgastrectomy; blood pressure 130/73 mm. Hg, FBS 84, BUN 18 mg./100 ml., bilirubin 0.5 mg./100 ml., cephalin flocculation 1 plus; autopsy revealed gastrointestinal hemorrhage
	14.32	11.5	0.661	21.7	12.1	7.20	...	10 O_2	
								11	
2,61	6.13	4.10	0.475	12.9	21.3	7.32	88	8 Na	Myocardial infarct, recovering uneventfully in three days; blood pressure 145/78 mm. Hg, FBS 90, BUN 17 mg./100 ml.; bilirubin 0.7 mg./100 ml.; autopsy revealed myocardial infarct
	6.05	4.03	0.472	12.8	22.2	7.34	...	10 Lactate 200	
	10.63	6.81	0.897	11.9	17.9	7.31	100	24 O_2 HCO_3 200	
	16.45	12.23	0.990	16.6	14.1	7.28	100	29 O_2 ...	
3,22	3.11	1.77	0.312	14.3	22.2	7.38	92	5-7 ...	Poliomyelitis, in respirator eight days, apparently doing well; blood pressure 150/90 mm. Hg, FBS 80, BUN 12 mg./100 ml.; autopsy revealed mild pneumonitis
	8.96	5.42	0.831	10.8	16.9	...	96	12 O_2	
	13.81	11.65	0.505	27.3	14.8	7.30	97	18 O_2 HCO_3 400	
								20 ...	
4,19	12.82	7.38	1.279	10.0	17.1	7.32	96	36 O_2	Poliomyelitis, in respirator twenty-one days, doing well, blood pressure 148/92 mm. Hg, FBS 98, BUN 14 mg./100 ml.; autopsy revealed pneumonitis and bronchial plugs
	14.36	9.41	1.163	12.4	16.9	7.36	...	48 O_2	
								52 ...	
5,54	22.40	16.95	1.281	17.5	...	7.18	...	18 O_2 HCO_3 400	Hypertension; blood pressure 180/110 mm. Hg, myocardial infarct, heart failure under control; digitalis, diuretics administered; FBS 75, BUN 40 mg./100 ml., SGOT 150 units; autopsy revealed pyelonephritis, myocardial infarct, pulmonary congestion
	23.67	18.40	1.238	19.1	7.9	7.18	97	24 O_2	
								30 ...	
	24.28	17.81	1.522	15.9	4.0	6.92	...	14 Na Lactate 300	
6,20	23.05	18.34	1.107	20.8	5.1	7.06	87	14½	Poliomyelitis, recovered in twenty days; streptococcal pneumonia, uneventful recovery, afebrile; FBS 100 and 75, BUN 15 and 18 mg./100 ml., PSP excretion 32 per cent (15 min.), BSP 10 per cent, bilirubin 0.4 mg./100, cephalin flocculation 2 plus, SGOT 35 units; autopsy revealed resolving pneumonitis
	17.14	11.56	1.312	13.1	11.9	7.30	100	24 O_2 HCO_3 400	
	15.47	9.08	1.502	10.3	14.8	7.34	...	26 ...	
	13.81	9.79	0.944	14.6	20.6	...	...	48 ...	
	18.64	12.14	1.528	12.2	12.8	7.33	...	72 ...	
	24.17	15.61	2.014	12.0	9.1	7.19	...	96 O_2 HCO_3 200	
	25.77	16.20	2.252	1.14	10.3	7.10	100	104 O_2	
								105 ...	
7,21	12.42	8.57	0.904	13.7	13.1	7.19	...	24	Poliomyelitis, bulbar, in respirator four days, intermittent respiratory distress; FBS 85, BUN 15 mg./100 ml., PSP 37 per cent (15 min.), BSP 5 per cent, bilirubin 0.3 mg./100 ml., cephalin flocculation negative, SGOT 20 units; autopsy revealed mild atelectasis and bronchitis
	18.57	12.43	1.444	12.9	8.9	7.16	93	29	
	19.20	11.82	1.736	11.1	11.7	7.22	100	32 O_2 HCO_3 400	
	22.55	17.24	1.247	18.1	7.8	7.00	100	48 O_2 HCO_3 200	
								52	
8,58	5.33	3.68	0.385	13.8	18.7	7.20	85	5 HCO_3 400 meq.	Pneumonia or pulmonary infarction, febrile, clearing uneventfully; blood pressure 140/85 mm. Hg; FBS 80, BUN 17 mg./100 ml., bilirubin 0.9 mg./100 ml., cephalin flocculation 1 plus; BSP 5 per cent, SGOT 30 units, LDH 100 units
	5.54	3.74	0.420	13.2	19.2	...	100	9 O_2	
	6.65	4.23	0.566	11.8	17.8	...	100	19 O_2 HCO_3 200	
								52	
	10.11	6.06	0.951	10.6	16.1	7.33	...	48 ...	
	7.93	5.13	0.656	12.1	18.0	...	97	72 ...	
	7.51	4.52	0.701	10.7	23.6	7.47	94	120 ...	
	9.92	6.04	0.911	9.2	...	...	92	132 ...	
	13.74	8.10	1.326	10.4	14.2	...	100	144 O_2	
	15.05	8.99	1.425	10.6	...	...	100	156 O_2	
	16.21	10.04	1.451	11.2	10.0	...	98	192 O_2	
	16.90	10.76	1.444	11.7	10.8	7.32	...	216 O_2	
	19.72	13.61	1.437	13.2	7.9	...	...	218 O_2	
9,48*	13.15	8.92	0.994	13.2	18.0	7.33	96	276	Old mitral regurgitation with failure; well controlled, S.B.E., treated, afebrile; icteric and cyanotic at onset; BUN 54

NOTE: L indicates blood lactate concentration, XL calculated excess lactate, P blood pyruvate concentrations, Sa_{O_2} arterial blood oxygen saturation, FBS fasting blood sugar, BUN blood nitrogen, BSP the percentage of injected bromsulfalein retained, LDH lactic dehydrogenase, and S.B.E. subacute bacterial endocarditis.

* We are indebted to Dr. William B. Schwartz of the New England Medical Center Hospital for the opportunity to study this patient who will be reported on in detail in the future.

TABLE II
SERUM ELECTROLYTE DATA*

Case No.	Day	Lactate (1.0) (mEq./L.)	UA (3) (mEq./L.)	Na^+ (144) (mEq./L.)	K^+ (4.0) (mEq./L.)	Cl^- (103) (mEq./L.)	HCO_3^- (25.0) (mEq./L.)	$\Delta L./\Delta[HCO_3^-]$ (mEq./L.)
2	1	10.63	11	143	4.1	101	17.9	9/7
3	1	8.96	10	144	3.9	104	16.9	8/8
4	2	14.36	14	137	3.8	93	16.9	13/8
6	1	23.05	24	142	4.0	100	5.1	22/20
...	2	13.81	15	140	4.0	91	20.6	13/5
...	3	18.64	20	136	4.1	90	12.8	17/17
...	4	25.77	27	137	4.2	87	10.3	25/15
7	1	12.42	14	145	4.0	105	13.1	11/12
...	2	22.55	24	134	3.8	89	7.8	22/17

NOTE: UA indicates the "unmeasured anion" before considering lactate; $\Delta L./\Delta(HCO_3)$ is the approximate ratio of change in serum lactate to change in serum bicarbonate (calculated as change from the normal values shown).

* Figures in parentheses represent normal values.

The first sign of lactic acidosis was usually hyperpnea with more or less marked tachypnea, and occasionally slight cyanosis. The patients usually also complained of weakness, fatigue and moderate to marked dyspnea in the early stages. The clinical syndrome progressed to stupor and finally death. The change in breathing, of course, was absent in the four patients whose breathing was maintained only by mechanical respirators. In the latter patients, as in most of the others also, a very low serum bicarbonate (total CO_2) was found by the clinical laboratory at the onset. The lungs were carefully examined physically, roentgenologically and, in some instances, bronchoscopically; but either no abnormalities were found or there were no changes from previous findings. No new neurologic changes were noted; the temperature and blood pressure were non-contributory, and the remainder of the physical examination and laboratory tests (blood counts, blood culture, urine and stool examination, electrocardiogram, venous pressure, circulation time) gave no clue to the cause of the change in any patient.

Laboratory. Blood hydrogen ion concentration was elevated in all the patients, as shown in Table I. P_{CO_2} was usually low. When sodium, potassium and chloride determinations were made, there was always an abnormally large discrepancy between the sum of anions and cations, which indicated the presence of some unmeasured anion in significant quantity. Table II shows the values found in five patients. Although the diagnosis of acidosis was established by these findings, blood sugar levels were normal (none of the patients had been diabetic previously), and no sugar or ketones were found in the urine. Azotemia was present in only two of nine patients, and no abnormalities of the blood urea or urinary sediment were found in the remainder. Therefore, in the ordinary clinical and laboratory findings, there appeared to be no explanation for the acidosis.

Lactate and Pyruvate. Blood lactate levels were markedly elevated in all the patients, as shown in Table I. Several of these patients exhibited the highest lactate concentrations ever observed in this laboratory, even in extreme hypoxia or physical exertion studied experimentally. As illustrated in Table II, the lactate ion accounted for all or nearly all the "unmeasured anion" of the serum electrolyte pattern. This finding suggests that lactic acid was almost entirely responsible for the acidosis, and that no significant quantities of any other acid were present.

The identity of the lactate estimated in the blood samples was further confirmed in several of the patients by various procedures. In six patients, blood acetaldehyde was repeatedly found to be zero. In two patients the lactate of the blood filtrate was identified by chromatography on silicic acid [2]. In six blood samples from four patients, the lactate found by analysis was demonstrated to be completely removed by the action of specific lactic dehydrogenase (in the presence of semicarbazide, and DPN at pH 9.5); the quantity of DPNH produced also roughly confirmed the quantity of lactate found by analysis.

Table I shows the levels of blood pyruvate

found in the patients with lactic acidosis. All the values were high, and some were extremely high, in terms of percentage change from normal; but they contributed only a minor amount of acid, generally about 1 mEq./L., to the acidosis. The elevation of pyruvate was not sufficient to account for the rise in lactate, as indicated by the large proportion of "excess lactate." Blood citrate [*4*] and α-ketoglutarate [*5*] showed an average increase of 175 per cent; but, even together with pyruvate, these minor ions usually totalled less than 2 mEq./L. "Total" keto acids [*3*] did not significantly exceed the sum of those mentioned, and total neutral ketones [*3*] were normal.

Blood Oxygen. As shown in Table I, in several of the patients arterial blood O_2 saturation was slightly or moderately depressed initially, probably from extreme tachypnea. However, 100 per cent oxygen was administered by face mask in all patients and resulted in full saturation of the blood throughout most of the course of the illness. P_{CO_2} was often slightly elevated in the early stage, but later was generally low, although not low enough to restore hydrogen ion concentration to normal. Arteriovenous oxygen differences across the leg or arm, or both, were estimated in four patients while circulation to the hand or foot was occluded with an inflated cuff. These values are shown in Table III. Other patients were studied on the same wards at nearly the same times and showed a mean femoral $(A\text{-}V)O_2$ of 54.2 ml./L. $\sigma = 7.1$, brachial 42.7 ml./L. $\sigma = 8$. By this comparison, therefore, the patients with lactic acidosis could not be shown to have reduced oxygen extraction from the blood. Blood O_2 dissociation curves were studied to some extent in two patients (Cases 4 and 7). The curves were significantly displaced to the right, as determined by two points (20 and 50 mm. Hg P_{O_2}). This was only an effect of the acidosis, as shown by two additional facts: (1) these curves coincided with the curves of blood from two normal subjects raised to the same hydrogen ion concentrations by the addition, respectively, of lactic and hydrochloric acids, and (2) the abnormal curves of the blood of these subjects were normal when the pH was raised to 7.4. The elevation of venous blood oxygen tension caused by the acid curve shift itself was only about 5 mm. Hg, and the beneficial effect was largely nullified by the slightly increased $(A\text{-}V)O_2$. Over-all rate of oxygen consumption was measured in two patients and found to be 165 and 150 ml./minute/M^2 surface area in one of them (Case 6, at sixteen hours and ninety-six hours) and 170 and 180 ml./minute/M^2 in the other (Case 8 on the fifth and eighth days). An open system with air was used, with Douglas bag and spirometer. These values are normal. Exchange ratios (R.Q.) were 0.95, 0.94, 0.97 and 0.95, respectively. Nutrition was derived almost entirely from carbohydrate and vitamins during the illness. This fact no doubt accounts for the high ratio of carbon dioxide production to oxygen consumption, since pulmonary ventilation was constant and the rate of rise of lactate in the blood extremely small.

TABLE III
MEASUREMENTS OF FEMORAL OR BRACHIAL BLOOD ARTERIOVENOUS OXYGEN CONTENT DIFFERENCE IN SEVERAL PATIENTS*

Case No.	C_{aO_2}	$(A\text{-}V)O_2$ ml./L.	
		Femoral	Brachial
2	182.4	63.4	57.3
3	204.0	68.9	...
6	196.5	...	53.6
	199.0	63.6	55.9
8	210.6	59.1	50.5
	202.5	64.7	55.6

* The arterial O_2 content (C_{aO_2}) is also given in each patient.

Miscellaneous Data. Tests of hepatic function were performed during the course of the lactic acidosis in five patients and four were within normal limits. One patient (Case 9) was slightly jaundiced. The tests included serum bilirubin, cephalin cholesterol flocculation and bromsulfalein excretion; determination of serum glutamic-oxalacetic transaminase was performed in three, and was elevated only in Case 5. Presumably, this occurred because of a recent myocardial infarct rather than because of hepatic disease; serum lactic dehydrogenase was normal in one patient (Case 8) but it was abnormal in Case 9, a patient with other evidences of hepatic disease. Blood urea was normal in all patients but two (Cases 5 and 8); in Case 5 there was a known pre-existing pyelonephritis and a mild stabilized azotemia (blood urea nitrogen 30 mg. per cent).

Course. Figure 1 illustrates the time course of the acidosis in one of the patients who survived

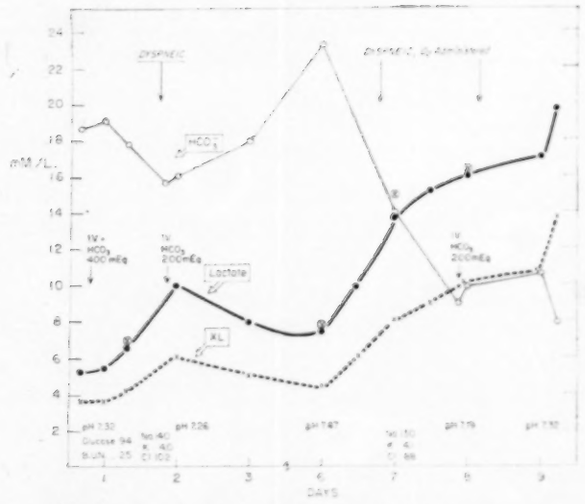

FIG. 1. The time course of lactic acidosis in one patient. The curves represent serum bicarbonate, serum lactate concentrations as measured, and calculated excess lactate (marked XL). Other values derived from arterial blood are shown along the bottom of the figure. The points indicated by a circled x are the calculated values of unmeasured anion from the routine electrolyte determinations [(Σ cations + 8) − (Σ anions + 25)].

longest. As noted in Table I, most of the patients died in one or two days after the onset (the time of onset was roughly judged from symptoms, in retrospect, and usually depended on the earliest change in breathing). The longest period of survival was twelve days. The ten day period depicted in Figure 1 does not show the steady progression suggested by some of the data in Table I. The first blood lactate values in this patient (Case 8) were only moderately elevated; but after an early period of worsening, the excess lactate level fell slightly, and the patient improved for four days. However, a progressive rise of blood excess lactate and (H^+) and fall of bicarbonate occurred in the last four days; death occurred after a sudden rise in blood lactate. This terminal, rapid rise in lactate was noted also in two other patients with lactic acidosis, but it was not seen in several patients who died of other causes [*1*]. Acidosis was usually extreme in the late stages but, as Figure 1 illustrates, near restoration of normal pH did not prevent the death of the patient. However, massive therapy with intravenous bicarbonate may have been responsible for more prolonged survival; the two patients who survived the longest (Cases 8 and 9) received the most alkali (Figure 1 and Table I). The administration of intravenous bicarbonate solution seemed surprisingly ineffective in some patients.

Examples of the ratios of change in serum lactate to change in serum bicarbonate are shown in Table II. Although these peak values developed in varying lengths of time, it is clear that the ratios are variable and only occasionally equal to unity. When only the rapid changes of lactate and bicarbonate in Table I are examined, it appears that a stoichiometric replacement of one by the other occurs only at low levels of acid. At high levels of acid other buffer systems appear to be much more important than bicarbonate; it seems likely that intracellular buffers are chiefly responsible. This was suggested by Turrell and Robinson [*7*] from their data on exercise, which we have been able to confirm for rapid changes during severe exertion. The probably generalized distribution of lactic acid in intracellular as well as extracellular spaces [*6,9,10*] may make this naturally occurring acidosis quite different from that induced in extracellular fluid by infusion of hydrochloric [*8*] or other mineral acids, which may actually produce intracellular alkalosis [*11*]. From these considerations it seems possible that some of the patients with lactic acidosis should have received far greater quantities of bicarbonate than were given when the pH was near 7, and that the small changes in serum bicarbonate brought about by such therapy are not surprising in view of the probable drop in the buffering capacity of intracellular proteins as hydrogen ion concentration decreased, that is, an "acid production" resulting from alkali therapy when intracellular buffers were freely involved. It is interesting to regard lactate as a carrier molecule for hydrogen ions crossing cell membranes, especially at low pH, in view of the obvious ease of movement of lactic acid across cell membranes. Table II shows that time is probably another influence on the ratios of acid to bicarbonate. As Table II and Figure 1 show, when a high lactate had been present for several days, serum chloride was reduced; thus a high bicarbonate persisted in spite of the continued lactatemia. Depression of serum chloride was not detectable when the disease progressed rapidly.

Oxygen inhalation had no effect on the course of lactic acidosis as far as could be determined. Positive pressure O_2 breathing was tried in three patients and seemed to be followed by unusually rapid deterioration and death. Sodium lactate, employed as alkali therapy in one patient (Case 2), caused no increase in blood lactate and appeared to have no harmful effect; but we

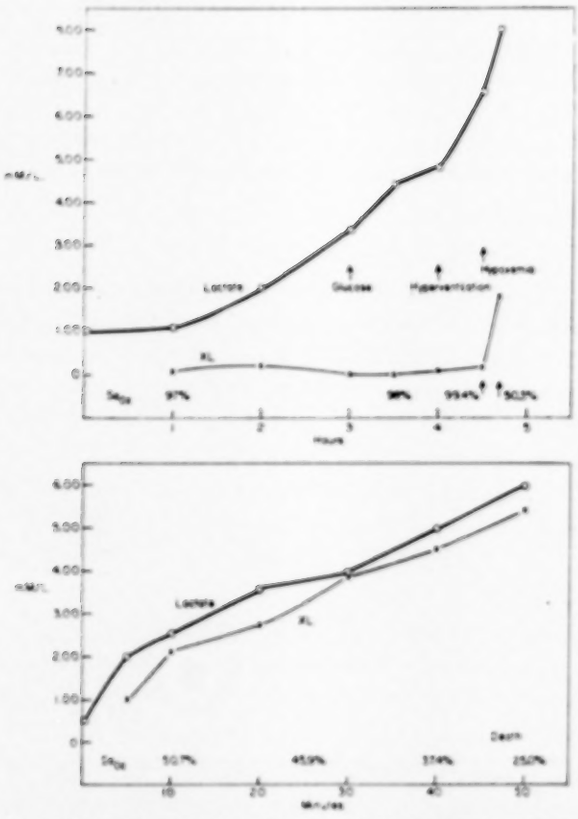

FIG. 2. Experimental hyperlactatemia in dogs. *Top*, effect of thiamine deficiency (injection of oxythiamine) and superimposed glucose infusion and hyperventilation produced with a respiratory pump. Five per cent O_2 in nitrogen was administered just prior to death. XL represents the excess lactate calculated from lactate and pyruvate increments. *Bottom*, effect of progressively increasing severity of hypoxemia produced by slow reduction of O_2 content of the inspired air; the ventilation was controlled to maintain an arterial blood pH of 7.35.

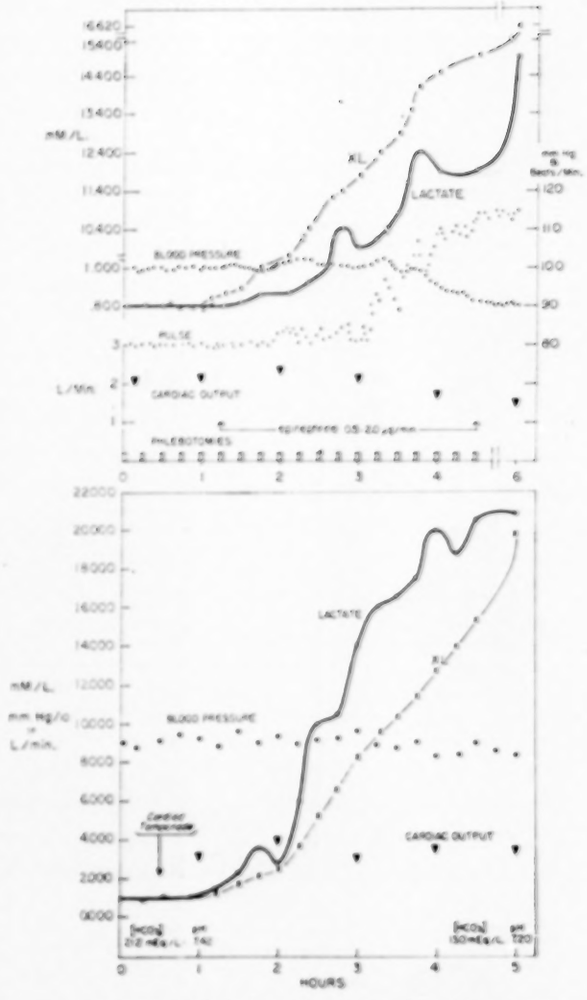

FIG. 3. Experimental lactic acidosis in dogs. *Top*, effect of very slow blood loss and intravenous infusion of epinephrine at varying rates sufficient to keep blood pressure normal but not less than .05 μg./minute. *Bottom*, effect of injecting plasma into the pericardium to produce cardiac tamponade at the highest pericardial pressure which had no effect on arterial blood pressure.

have avoided its use in these patients as a general rule.

Autopsy findings (Table 1) were varied and usually not insignificant because the patients had all been hospitalized for major illnesses before the lactic acidosis occurred. The autopsy findings, however, revealed no common factors among these patients, and in a few instances did show only minor changes.

Experimental Lactic Acidosis. Figure 2 illustrates a very common finding in the numerous instances of lactatemia which have been produced in experimental animals by many different means: the findings of clinical lactic acidosis are very difficult to reproduce. Relatively high blood lactates can be produced by the stimuli which cause primary pyruvate accumulations [6], as shown in Figure 2 (*top*), or by combinations of these various stimuli with hypoxia and, in addition, "excess lactate" accumulation. But achievement of the extreme levels of blood lactate occurring in the patients was very difficult if the proportion of excess lactate was required to account for more than 60 per cent of the lactatemia, as it did in the patients.

Figure 2 (*bottom*) illustrates the relative ineffectiveness of hypoxemia in producing extreme lactic acidosis. Death occurred in such animals before the magnitude of accumulation of lactate simulated that of the clinical condition. However, we have been impressed in the past with

the much greater effectiveness of circulatory collapse in producing lactatemia, and therefore employed this method (Fig. 3) to produce a lactic acidosis which resembled that found in the patients of "group 2B" [*1*], that is, extreme lactic acidosis due largely to excess lactate, but associated with normal blood oxygen content and normal blood pressure. The required changes were induced in dogs during slow blood loss (Fig. 3, *top*) or slowly developing cardiac tamponade (Fig. 3, *bottom*) especially if catecholamines were administered. As the figures illustrate, the excess lactate change in the five experiments of this kind was the earliest indication of the circulatory events which subsequently became obvious. The circulatory deterioration eventually became identifiable in the measurements in the following order: (1) cardiac output, (2) pulse rate, and (3) blood pressure. Inhalation of 100 per cent oxygen, having no effect on the circulatory change, did not alleviate the tissue hypoxia or significantly delay the excess lactic acidosis.

COMMENTS

The studies of this small number of patients with a rare form of metabolic acidosis are fragmentary at present. The types of data which were obtained are needed at closer intervals and greater regularity; no measurements of cardiac output and no detailed peripheral vascular evaluations have been obtained, although their pertinence is suggested by considerations to be mentioned. Various trials of therapy would probably be of value in shedding light on the syndrome. The deficiencies in our knowledge arise in part from our inability to recognize the disease clinically, and in part from its rapid termination after it is recognized. It is clear that even if the disease occurred in a patient under observation at a hospital, it would remain obscure unless a blood lactate analysis were performed. Therefore the possibility exists that lactic acidosis is more common than it now appears to be. The present series suggests that the disease occurs only in patients who are already hospitalized for other, apparently unrelated causes; this appearance may be an artifact since the diagnosis would not be likely to be made under other circumstances.

Another suggestion arises from this series which may also be an artifact of selection. Four of the nine patients had poliomyelitis; but after the first of these was discovered, every patient was studied who was admitted to an active infectious disease service during a polio epidemic (1955); the great majority showed no sign of lactic acidosis of type 2B. No other survey of this intensity has been carried out, and the series may therefore be weighted. It is possible that there is some more significant relationship between lactic acidosis and poliomyelitis itself, or between lactic acidosis and generalized paralysis, or the use of mechanical respirators; but in the five remaining patients of this series no similar factors were found and, therefore, the inference is not drawn at this time.

Similarly there was definite kidney disease in one patient, definite liver disease in one, and significant heart disease in three patients. But each of these possible broad etiologies of lactic acidosis was almost certainly absent in the majority of the patients. Thus, from the point of view of clinical and morphologic evidence, no sound conclusions about the pathogenesis of the condition seem warranted until more observations are available. The cause remains unknown.

A theoretical lead may be followed, however, for the time being. Various pieces of evidence suggest that the accumulation of "excess lactate" in the body may be interpreted as an indication of the anaerobic metabolism which results from deficiency of tissue oxygen supply relative to requirements [*1*]. This theory would account for the findings in the patients of group 2 on the basis of widespread tissue hypoxia. Although there is no independent means for determining the presence of such hypoxia in patients, several of the possible causes of hypoxia can be diagnosed. Hypoxemia is the easiest of these to rule out. Lactic acidosis was found to proceed unabated in the presence of normal arterial oxygen content and capacity. A normal oxygen dissociation curve of the blood was established in only two patients, but normal or increased oxygen extraction from blood was found for major tissue masses in four others, that is, femoral and brachial arteriovenous differences were not reduced.

Hypoxemia, even when present, is subject to circulatory compensations which reduce or prevent tissue hypoxia. However, ischemia presents greater possibilities as a cause of the hypoxia. But a generalized reduction of blood flow in the body seems a less attractive possibility than local reductions in perfusion, for two

reasons. First, very marked reductions in cardiac output are seen in some patients with congestive heart failure, especially with mitral valvular regurgitation, and they do not result in elevated blood lactate [*12*]. Second, no clinical evidence of extreme reduction of cardiac output was found in the patients with lactic acidosis. There was no evidence of heart failure; radial arterial pulses were strong, chest wall impulses forceful, and arterial blood pressure and pulse pressure normal or slightly elevated until the terminal stages. However, the cardiac output has not been measured as yet in patients with lactic acidosis.

Several hypothetical causes of hypoxia could not be substantiated by the measurements of arteriovenous blood oxygen differences, although they were not ruled out by such data. The presence of normal or somewhat elevated values is opposed to any inability of oxygen to (1) cross capillary membranes, (2) cross cell membranes, or (3) to react with cytochrome oxidase.

No clinical information is available to rule out the idea that a peripheral vascular phenomenon may have produced oxygen lack in major tissue areas and resulted in accumulation of the products of anaerobic metabolism. However, evidence which would definitely support this hypothesis is also scanty. All four patients with poliomyelitis exhibited the patchy skin color changes occasionally seen in this infection, varying between pallor, flush and cyanosis. Whether or not the circulatory effects of a body respirator may also have contributed to circulatory embarrassment in these patients cannot be stated. No evidence of abnormal superficial vascular activity was noted in the other patients. The only additional evidence which might bear on the question of pathogenesis is the important implication of the animal studies. The anaerobic metabolism which occurs in frank peripheral circulatory failure cannot be called upon to account for clinical lactic acidosis because frank circulatory collapse had obviously not occurred. But the data from the animal studies illustrate the fact that an earlier stage of adjustment, presumably circulatory, may occur. In this period anaerobic metabolism is active, but no other detectable effects of the altered circulation have yet appeared. It may indeed be this adjustment, with its associated peripheral vasoconstriction, which prevents the occurrence of frank circulatory collapse at this stage. But even if such an explanation reasonably accounted for the findings in experimental animals, its application to the patients would be hypothetical, inasmuch as there were no inciting factors in some of the patients which could be considered comparable to those in the experiments. Such tissue hypoxia of ischemic origin would be little affected by the inhalation of O_2, since slightly increasing a normal blood O_2 content without improving blood supply to the tissues concerned would alter O_2 delivery very little. The exact role of epinephrine and norepinephrine in the animal experiments is not yet clear; similar results were sometimes obtained without exogenous catecholamines, but not so consistently. Depressive ether anesthesia appears to be capable of producing unusual degrees of lactate accumulation [*13*], as we can confirm. Brewster et al. have presented evidence of an important role of catecholamines in this phenomenon [*14*]. In two of the patients with lactic acidosis, normal plasma levels of epinephrine and norepinephrine were found; however, the plasma concentration *per se* might not be pertinent to this question.

SUMMARY

1. A group of nine patients was observed with a syndrome of marked hyperpnea, tachypnea and dyspnea, with weakness and fatigue, progressing to stupor and finally to death in periods ranging from a few hours to twelve days.

2. All the patients had low serum bicarbonate, sometimes extraordinarily low, an abnormally acid pH of the blood, and a high value of unmeasured anion in the serum electrolyte pattern. Nevertheless, they did not have diabetes or renal failure and had not been exposed to any toxic agents.

3. The unmeasured anion of the serum of these patients was found to be lactate; extreme elevation of blood lactate was a consistent and nearly unique feature of this condition.

4. Although none of the patients was without disease before the onset of lactic acidosis, and some were recovering from serious diseases, they apparently had no features of past history in common and, therefore, none with which the subsequent hyperlactatemia could be said to be associated.

5. The biochemical cause of the accumulation of lactic acid appeared to be widespread tissue hypoxia, but the causes of such hypoxia remained obscure. However, the chemical syn-

drome could be reproduced in animals only by gradual peripheral circulatory failure, and this possibility could not be ruled out in the patients.

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The Neurologic Basis of Cheyne-Stokes Respiration*

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WHETHER Cheyne-Stokes respiration (CSR) is neurogenic, cardiogenic or a combination of both has been argued since John Cheyne [*1*] first described respiratory periodicity in a patient with both a diseased heart and "enlarged cerebral ventricles." Both past and recent clinical and autopsy studies [*2–5*] demonstrate that the overwhelming majority of subjects with CSR show neurologic dysfunction and morphologic abnormalities of the brain. However, such inferential evidence does not exclude associated cardiovascular defects as causing the respiratory disturbance.

Four major theories, at least partially incompatible with each other, have been advanced to explain periodic breathing: (1) that CSR is due to circulatory delay and is a sign of heart failure; (2) that CSR is due to cyclic medullary depression; (3) that CSR is due to medullary hyperexcitability (with intermittent periods of fatigue); and (4) that CSR arises when supramedullary respiratory influences are altered.

Prior to Traube [*6*], studies on ventilatory periodicity were limited to identifying the associated tissue pathology. Traube, and later Filehne [*7*], focused on the apneic cycle, which they took to represent medullary insensitivity. In 1877, while Traube and Filehne were arguing minor differences, Francois-Franck [*8*] described apneic periods following forced hyperventilation in normal man. Cuffer [*9*] repeated and confirmed this work, concluding that the apneic period of Cheyne-Stokes respiration resulted from excessive ventilation. Rosenbach [*10*] also suggested that increased rather than decreased irritability of the medullary respiratory center was responsible for generating CSR: apnea represented fatigue following the increased cellular activity.

Biot [*11a*] and Hein [*11b*] proposed that breathing abnormalities associated with medullary dysfunction were not CSR since medullary damage in animals produced intermittent but not truly periodic breathing. Wellenbergh [*12*], describing experiments in which elevating the intracranial pressure produced intermittent breathing, was also reluctant to equate this with human CSR. Marckwald [*13*] uniformly failed to produce true respiratory periodicity in experimental animals by damaging the lower brain stem; he concluded that human CSR was probably not a consequence of medullary dysfunction, and occurs only when "higher centers cease to act."

Subsequent investigators have not always heeded Marckwald's analysis. Both Eyester [*14*] and Cushing [*15*], for example, equated the intermittent breathing produced by increased intracranial pressure with periodic breathing, and concluded that CSR reflects medullary depression.

In 1909 Douglas and Haldane [*16*] demonstrated that following voluntary hyperventilation normal men breathe periodically for short periods of time. Douglas and Haldane also demonstrated that sustained respiratory periodicity sometimes results when normal men are exposed to fluctuating anoxemia plus hyperventilation alkalosis, citing Mosso's observation that mountain climbers sometimes breathe periodically at high altitudes.

Pembry and Allen [*17*] demonstrated that the alveolar respiratory gases fluctuated in CSR, just as did the ventilation itself. Later, Anthony et al. [*18*] confirmed these cyclic gas changes in the arterial blood, demonstrating maximal arterial CO_2 tensions coinciding with peak ventilation. From these results and his own data, Harrison [*19*] concluded that, at least in regard to CO_2, subjects with periodic breathing were

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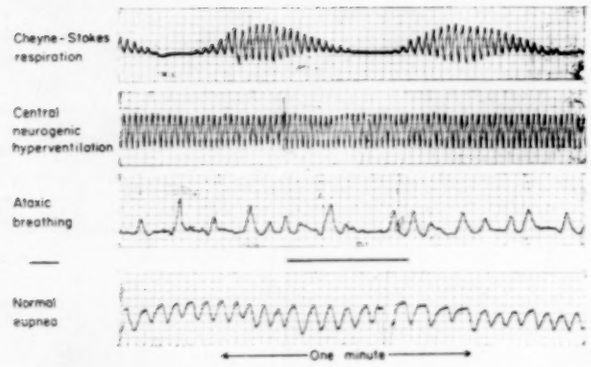


FIG. 1. Pneumographic comparison between CSR and other neurogenic ventilatory abnormalities: CSR is marked by regular waxing and waning with periodically placed apneic periods of approximately equal length. Central neurogenic hyperventilation (CNH), which is metronomically regular and usually rapid, is seen with pontine lesions [*21*]. Ataxic breathing occurs with medullary failure. This example is from a case of bulbar poliomyelitis [*38*]. Though occasionally confused with CSR, the irregular irregularity of ventilatory ataxia is clear upon close inspection.

overventilating. The source of hyperventilation, Harrison believed, lay in excessive, reflex, respiratory stimulation from the lungs.

Guyton [*20*] has experimentally produced respiratory periodicity by changing the circulation. By lengthening the carotid arteries of dogs, Guyton greatly delayed the heart-to-brain circulation (120 to 300 seconds). In one-third of the animals periodic breathing spontaneously developed; in the remaining, it was necessary to initiate CSR by mechanical hyperventilation. Guyton likened the respiration to a servomechanism in which feedback delay leads to oscillation. Although no blood reached the brain through normal circulatory pathways, Guyton made no comment upon how much neurologic damage resulted from the changes he induced, and the postoperative neurologic function of his dogs was not mentioned.

Jackson [*2*] long since had observed that bilateral cerebral infarction frequently produces CSR. Recently Talbert et al. [*3–5*] extended this "neurologic fragment," noting that patients showing CSR invariably had anatomic abnormalities of the brain at autopsy; this occurred whether or not circulatory dysfunction had dominated the clinical picture. The most common lesion was bilateral cerebral infarction, which was found in eleven of thirteen cases [*5*]. The other two subjects had grossly evident unilateral infarctions. Clinical appraisal of the function of the other cerebral hemisphere and microscopic sections of the apparently uninvolved side were not reported upon in these two cases.

Plum and Swanson [*21*] observed that sustained hyperventilation (central neurogenic hyperventilation) frequently follows acute damage to the central pontine tegmentum of man. CSR frequently preceded the development of continuous hyperpnea in these cases and appeared to result from brain dysfunction located rostral to the pons. As Harrison had previously emphasized, respiratory alkalosis was present in patients with CSR but was less intense than that associated with central neurogenic hyperventilation.

Plum and Swanson's observations [*21*], as well as those of Talbot, Currens and Cohen [*3*], shed doubt on the medullary origin of CSR—a doubt Marckwald had expressed half a century earlier. Similarly, the extraordinary circulatory delay required for Guyton's dogs to breathe periodically suggested limited applicability to human disease. Accordingly, additional clinical and physiologic data were obtained to explain the genesis of periodic breathing in man. The accumulated data indicate that, whatever the associated cardiac change, neurologically altered respiratory sensitivity to CO_2 is required to produce Cheyne-Stokes respiration.

MATERIAL AND METHODS

Twenty-eight patients were studied who demonstrated typical waxing and waning of ventilation regularly interspersed with at least brief periods of apnea. (Fig. 1.) Twenty-six patients had periodic breathing while awake, whereas two showed CSR only during sleep. Considerable (although unsuccessful) effort was made to find patients with periodic breathing who lacked clinically demonstrable neurologic abnormalities. Most patients studied were old and seriously ill; half of them died during hospitalization. Control studies were performed on four groups with regular breathing: four patients with bilateral cerebral vascular disease, three neurologically intact patients with congestive heart failure producing hypoxemia and prolonged circulation time, three patients with unilateral strokes, and four apparently normal young adults.

All patients had careful clinical examinations, roentgenograms of the chest, electrocardiograms, and determinations of venous pressure.

Circulation times were measured employing an ear lobe oximeter, adjusted to respond to methylene blue dye. A few patients were alert enough to recognize the standard Decholin® arm-to-tongue end point.

Arterial bloods were drawn from indwelling brachial or femoral needles. The pH was determined on freshly drawn blood at 37°c. using a Coleman electrode attached to a Cambridge Model R pH meter. Arterial oxygen saturations and carbon dioxide contents were determined by Van Slyke and Neill's manometric technic. Arterial oxygen tensions (PaO_2) were calculated from the nomograms of Dill [*22*], and Henderson [*23*]. Carbon dioxide tension ($PaCO_2$) was calculated from the monogram of Singer and Hastings [*24*].

Pulmonary ventilation was measured by either of two methods: During studies of sensitivity to CO_2, expired air was collected as will be described. For the remaining ventilatory studies a pneumotachometer was connected to a mouthpiece and the oscillographic output was integrated planimetrically, the output of a full minute being calculated. Alveolar ventilation V_A was estimated using a deadspace of 150 cc.

To determine the ventilatory response to CO_2 (sensitivity to CO_2) patients breathed three different concentrations of CO_2 (2 per cent, 3 per cent and 5 per cent) in oxygen. Base line ventilation was taken at the concentration of gas which just eliminated respiratory periodicity. Expired air was collected continuously in a Tissot spirometer and alveolar CO_2 tensions ($PaCO_2$) were monitored continuously by an infrared analyzer (Liston-Becker) for twenty minutes or until ventilatory stability was reached, whichever was longer. Minute ventilation was taken as the mean of the last three minutes of collections, arterial blood being drawn simultaneously for determining $PaCO_2$. The stimulus-response curve was then constructed by plotting estimated minute V_A against $PaCO_2$.

Respiratory threshold for CO_2 (or apneic point), was defined as the arterial CO_2 tension just sufficient to stimulate respiration in a fully oxygenated subject. This point was determined by regression of the CO_2 stimulus-response curve to its intercept with theoretical apnea. The validity of this method was verified by using oxygen and mechanically hyperventilating unconscious subjects to apnea: as breathing began $PaCO_2$ was determined. Thresholds determined in three cases by both methods agreed within 1 to 2 mm. Hg. Oxygen therapy abolished periodic breathing in approximately half the cases studied; in cases in which periodic breathing was not abolished, oxygen was administered and the apneic point was checked by measuring $PaCO_2$ coincidentally with the outset of ventilation.

To show the relative stimulation which $PaCO_2$ and PaO_2, respectively, contributed to respiration through a wide range of ventilation, isoventilation curves were constructed on five patients. Three points of equal ventilation, each associated with different CO_2 and oxygen values were determined by simultaneously measuring $PaCO_2$, PaO_2 and breath-to-breath tidal volume. Since the blood gases differed at similar ventilations, two points were obtained during quiet breathing on the crescendo and decrescendo limbs of the CSR respiratory cycle. The third point was obtained during a determination of sensitivity to CO_2. The three points were then plotted and interconnected on Rahn and Fenn's PaO_2-$PaCO_2$ coordinate grid [*25*]. This isoventilation curve described the combined PaO_2-$PaCO_2$ values which resulted in equal minute ventilation. Four curves were drawn for each patient to indicate the relative stimulation provided by PCO_2 and PO_2 through a wide range of ventilation.

RESULTS

Clinical Findings. Every patient showing CSR had clinical signs of extensive brain disease. (Table 1.) Only rarely were the neurologic signs subtle. Twenty-five patients showed bilateral "pyramidal" signs, most frequently manifested by pseudobulbar palsy. Two subjects had organic dementia together with increased stretch reflexes in the extremities. One patient was obtunded and demented but lacked specific abnormalities of the motor system. This high incidence of neurologic abnormalities did not reflect bias in selecting patients for physiologic study. During an eight month period every patient on the medical service who had periodic breathing was examined clinically. There were forty-five such patients, twenty-eight of whom made up the study group. None of the remaining seventeen lacked neurologic changes similar to those found in the physiologically studied group.

Cardiovascular abnormalities were frequently but not invariably found in the twenty-eight cases. (Table 1.) Five patients had no cardiovascular disease detected by history, physical examination, electrocardiogram, roentgenograms of the chest or circulation time. Eight patients showed circulatory decompensation with pulmonary engorgement, cardiomegaly, increased systemic venous pressure or peripheral edema. Fifteen other patients showed cardiac abnormalities such as arrhythmia or electrocardiographic evidence of myocardial disease, but they had no clinical evidence indicating circulatory decompensation. Circulation times were measured in twelve subjects with periodic breathing, and in seventeen control subjects. (Fig. 2.) The mean circulation time in CSR was prolonged over normal and elderly control subjects, but not over control subjects with congestive heart failure. Several subjects with CSR had circulation times less than fifteen seconds, and most were less than twenty seconds.

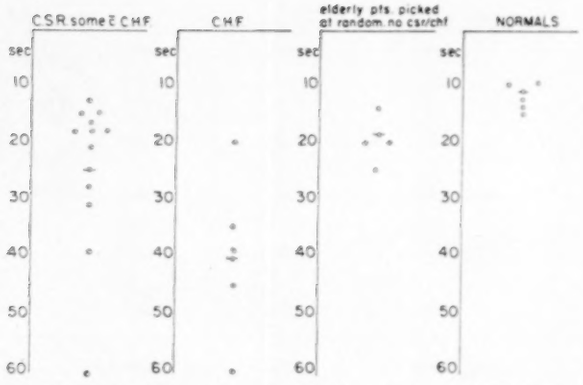


FIG. 2. Circulation times in CSR and control subjects. Mean = ⊖.

Five patients with CSR were autopsied. The postmortem findings are summarized in Table II and Figure 3. The subjects all showed bilateral cerebral hemispheric infarcts, and many had brain stem lesions as well. The abnormalities were distributed too diffusely to localize the significant neurological changes responsible for inducing periodic breathing. However, all subjects showed lesions involving the descending "pyramidal" motor pathways involving corona radiata, internal capsule or basis pontis.

Blood Gas Studies. Nineteen of the twenty-eight subjects showing CSR had blood gas

TABLE I

CLINICAL NEUROLOGIC AND CARDIOVASCULAR FINDINGS IN TWENTY-EIGHT PATIENTS WITH CHEYNE-STOKES RESPIRATION

No. of Patients	Findings
	Neurologic
25	Bilateral disease of the motor pathway (snouting, spasticity, positive Babinski signs, etc.); (9 typical pseudobulbar palsy)
2	Subtle bilateral motor pathway signs together with dementia
1	Obtundation and dementia
	Cardiovascular
15	Organic heart disease without failure { Left ventricular hypertrophy (10 cases) * { Healed myocardial infarct (2 cases) * { Auricular fibrillation (4 cases) *
8	Congestive failure Venous pressure > 100 mm. H_2O (5 cases) Myocardial infarction (5 cases: 2 subacute, 3 healed) Pulmonary edema (4 cases)
5	No heart disease

* Electrocardiographic findings.

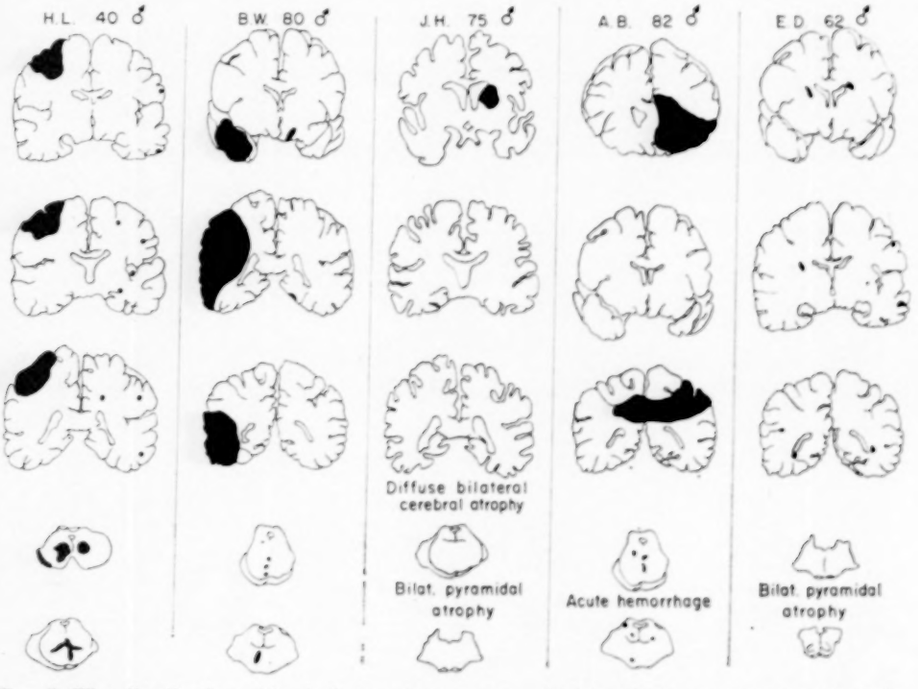


FIG. 3. The distribution of brain lesions in five cases. (Table II.) Except for atrophy of the pyramidal tract the two brain stems were normal; in another instance damage to the brain stem was terminal, postdating the time when periodic breathing was observed.

determinations with analyses being made at from 2 to 5 points along the cycling respiratory curve. (Table III.) Bloods were drawn during either a single or two consecutive respiratory cycles. All nineteen subjects showed respiratory alkalosis. The arterial pH fell below 7.4 only once (in patient A. Bi. in whom the pH cycled between 7.52 and 7.38). The pH values were highest during apnea, and lowest at peak ventilation. Arterial carbon dioxide tensions were invariably reduced and ranged between 21 and 40 mm. Hg, varying reciprocally with the pH. During the respiratory cycle individual patients had $PaCO_2$ shifts as little as 6 mm. Hg, and as great as 17 mm. Hg. Blood oxygen saturation varied considerably from patient to patient, with peak saturation levels ranging from 97 per cent to 89 per cent. The saturation fluctuated, being lowest at mid-hyperventilation and highest at mid-apnea. Physiologic desaturation was not invariable: arterial oxygen saturation in one case remained always above 94.3 per cent and in another case always above 92 per cent.

Because of pH shifts, calculated arterial oxygen tensions cycled differently from O_2 saturation. (Table III, Fig. 4.) The PaO_2 values fell during the respiratory crescendo, remained comparatively low throughout the respiratory phase, and rose coincidentally with the onset of apnea. (Fig. 4.) Since blood alkalosis persisted throughout both hyperpnea and apnea, the Bohr effect [*26*] kept PaO_2 subnormal (at levels

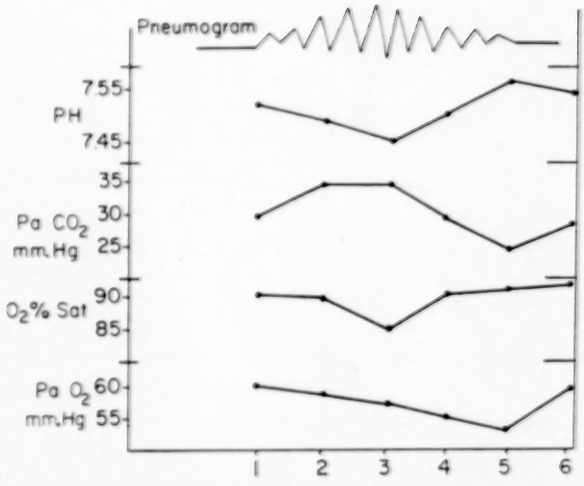


FIG. 4. Relationship of blood gases to respiratory cycle. As respiratory decrescendo proceeds, O_2 tension falls (lower line), despite increasing arterial O_2 per cent saturation. Points shown are mean data from Table III.

which, although fluctuating, insured continuous chemoreceptor stimulation [*27*]) despite comparatively higher arterial blood saturations. For example, the highest PaO_2 observed in any subject was 78 mm. Hg and this was at a time when his arterial saturation was 97 per cent.

Pulmonary Ventilation. Ventilatory volumes were measured in six cases. (Table IV.) Despite periodic apnea, total resting minute alveolar ventilation was uniformly elevated, ranging from 4.4 to 14 L./minute. Peak tidal volumes ranged from 450 to 800 cc.

TABLE II

ABNORMALITIES OF THE BRAIN, HEART AND LUNG FOUND AT AUTOPSY OF PATIENTS WITH CHEYNE-STOKES RESPIRATION

Patient, Age (yr.) and Sex	Heart	Lungs	Brain
H. L. (40 ♂)	Left ventricular hypertrophy, coronary atherosclerosis, myocardial infarct (3 wk.)	Pulmonary edema	Gross left cerebral infarct; multiple tiny right cerebral infarct; midpontine infarct
B. W. (80 ♂)	Normal myocardium	Normal	Massive hemorrhagic left cerebral infarct; transtentorial compression of right cerebral peduncle; pontine infarct.
J. H. (75 ♂)	Left ventricular hypertrophy	Normal	Right cerebral infarct (caudate and putamen); bilateral advanced cerebral atrophy
A. Bi. (82 ♂)	Coronary atherosclerosis, myocardial infarction (terminal)	Multiple pulmonary emboli (terminal)	Massive bilateral cerebral infarcts; brain stem hemorrhage (terminal)
E. D. (62 ♂)	Old myocardial infarct	Normal	Bilateral cerebral infarcts; brain stem normal

TABLE III

ARTERIAL BLOOD DATA IN CHEYNE-STOKES RESPIRATION

Patient	Blood Samples for Individual Patients	Portion of Respiratory Cycle in Which Blood Drawn					
		End Apnea	Mid-Crescendo	Mid-Hyperpnea	Mid-Decrescendo	Beginning Apnea	Mid-Apnea
		1	2	3	4	5	6
A. McC.	pH	...	7.50	...	...	7.54	7.50
	PCO_2*	...	35.5	...	...	31.0	33.0
	PO_2*	...	57.0	...	...	62.0	70.0
	O_2% saturation	...	90.9	...	...	94.4	95.4
H. P.	pH	7.53	...	...	...	7.51	...
	PCO_2	26.0	...	...	...	24.5	...
	PO_2	59.0	...	...	...	60.0	...
	O_2% saturation	93.4	...	...	...	93.4	...
W. Wa.	pH	7.53	...	...	...	...	...
	PCO_2	36.0	...	...	...	...	...
	PO_2	...	...	...	...	...	...
	O_2% saturation	81.6	...	69.2	...	84.3	87.2
T. C.	pH	7.54	7.46	7.49	7.55	7.58	...
	PCO_2	32.0	39.0	36.0	28.8	27.5	...
	PO_2	...	62.0	55.0	54.0	54.0	...
	O_2% saturation	...	90.8	90.9	94.6	94.2	...
W. Wc.	pH	7.47	7.43	7.40	7.45	7.53	7.48
	PCO_2	36.0	...	39.0	...	30.5	36.5
	PO_2	65.0	...	62.0	...	58.0	70.0
	O_2% saturation	93.0	...	91.4	...	92.0	94.3
C. Z.	pH	7.49	...	7.43	...	7.57	7.58
	PCO_2	31.5	...	40.0	...	26.0	25.0
	PO_2	57.0	...	52.0	...	46.0	54.0
	O_2% saturation	91.0	...	87.5	...	89.2	94.3
A. K.	pH	7.55	7.49	7.49	7.58	7.59	...
	PCO_2	29.0	31.5	34.0	29.5	26.0	...
	PO_2	58.0	55.0	55.0	58.0	52.0	...
	O_2% saturation	94.0	91.3	91.5	94.9	95.0	...
A. Bo.	pH	7.52	7.41	7.40	7.38	7.47	...
	PCO_2	29.5	37.5	38.0	37.5	31.0	...
	PO_2	...	...	...	...	...	...
	O_2% saturation	...	...	...	...	...	...
A. P.	pH	7.57	7.48	7.45	7.52	7.65	...
	PCO_2	23.5	29.8	34.5	25.8	21.0	...
	PO_2	79.0	68.0	72.0	66.0	59.0	...
	O_2% saturation	97.0	93.4	94.3	94.3	95.6	...
N. H.	pH	7.43	7.41	7.39	7.49	7.52	...
	PCO_2	25.8	37.2	39.6	29.6	27.0	...
	PO_2	57.0	60.0	54.0	47.0	46.0	...
	O_2% saturation	89.9	89.0	84.0	85.0	87.0	...

* PCO_2 and PO_2 expressed in mm. Hg.

TABLE III—(*Continued*)

ARTERIAL BLOOD DATA IN CHEYNE-STOKES RESPIRATION

Patient	Blood Samples for Individual Patients	Portion of Respiratory Cycle in Which Blood Drawn					
		End Apnea	Mid-Crescendo	Mid-Hyperpnea	Mid-Decrescendo	Beginning Apnea	Mid-Apnea
		1	2	3	4	5	6
T. B.	pH	7.61	7.54	...	7.56	...	7.67
	PCO_2	27.0	33.0	...	30.0	...	23.0
	PO_2	47.0	48.0	...	...	...	45.0
	O_2% saturation	92.0	87.0	...	...	...	89.0
A. G.	pH	7.50	...	7.44	7.49	7.52	...
	PCO_2	23.0	...	29.5	24.0	22.0	...
	PO_2	55.0	...	53.0	51.0	50.0	...
	O_2% saturation	93.2	...	88.5	90.8	91.0	...
E. D.	pH	7.53	7.51	...	...	...	...
	PCO_2	23.5	25.5	...	...	...	...
	PO_2	...	...	...	...	...	...
	O_2% saturation	94.3	87.1	...	...	...	...
A. B.	pH	7.56	...	7.51	...	...	...
	PCO_2	22.0	...	25.5	...	...	...
	PO_2	...	...	...	...	...	...
	O_2% saturation	70.0	...	64.8	...	...	...
L. J.	pH	...	...	7.53	...	...	7.49
	PCO_2	...	...	30.2	...	...	32.2
	PO_2	...	...	...	...	...	...
	O_2% saturation	...	...	92.9	...	...	98.8
J. H.	pH	...	7.46	...	...	7.51	...
	PCO_2	...	41.1	...	...	27.3	...
	PO_2	...	...	...	...	...	...
	O_2% saturation	...	91.3	...	...	95.2	...
B. W.	pH	7.50	7.47	7.47	...	7.57	7.55
	PCO_2	29.0	32.0	32.0	...	22.5	24.0
	PO_2	60.0	55.0	55.0	...	56.0	59.0
	O_2% saturation	93.4	89.9	88.8	...	93.6	93.0
Mean	pH	7.52	7.47	7.45	7.50	7.55	7.54
	PCO_2	29.0	34.2	34.4	29.3	24.1	28.9
	PO_2	60.0	58.0	57.0	55.2	53.4	60.0
	O_2% saturation	90.2	90.1	85.8	91.9	92.0	93.0

The Cause of Hyperpnea in CSR. Both the respiratory alkalosis and elevated V_A values cited indicate that CSR is marked by over-all hyperventilation. Three alternatives were entertained to explain the overbreathing: (1) that it was due to anoxemia; (2) that it was due to increased pulmonary stretch receptor stimulation; or (3) that it was due to increased central respiratory excitability. To test these alternatives, ventilation and blood gases were measured during oxygen therapy; respiratory CO_2 thresholds were determined after eliminating anoxemia, and ventilatory CO_2 sensitivity was measured.

Effect of O_2 breathing: Six subjects had minute alveolar ventilation and blood gases measured

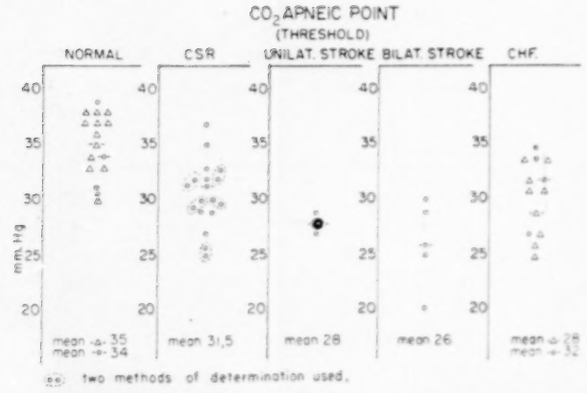


FIG. 5. Apneic points in CSR and control subjects. Each point represents the $PaCO_2$ coinciding with apnea. Points connected in loops represent apneic points determined by two methods in the same patient. All subjects had arterial O_2 saturation >100 per cent at the time of determination. △ = data from literature [28]. 0 = data from this laboratory.

during oxygen therapy. (Table IV.) Ventilation was above normal (mean V_A 7) and respiratory alkalosis continued despite arterial oxygen saturations exceeding 100 per cent. Oxygen therapy in three of these six subjects reduced V_A 25 per cent below resting (room air) levels. This was greater than the expected 10 to 15 per cent reduction experienced by normal subjects on oxygen therapy and appeared best explained by the low oxygen tensions found in these subjects on room air. (Table III.)

TABLE IV
VENTILATION VOLUMES IN CHEYNE-STOKES RESPIRATION

Patient	Room Air			100% O_2		
	V_A	Peak Tidal Volume	Respiratory Rate	V_A	$PaCO_2$	pH
L. H.	8.4	700	24	...	...	...
W. F.	4.4	450	20	...	...	...
A. D.	8.1	...	...	...	...	...
H. L.	9.0	650	27	8.0	26	7.46
L. R.	14.0	800	25	7.9	31.5	7.50
A. K.	7.0	700	19	5.4	33.5	7.55
B. M.	...	...	...	3.9	30.5	7.49
H. P.	...	...	...	5.1	30.0	7.49
R. P.	...	...	...	4.9	34.5	7.46
Mean	8.5	...	...	7.0	...	...

NOTE: The administration of O_2 diminished but did not abolish hyperventilation.

CO_2 thresholds (apneic points): If anoxemia is eliminated, the presence and magnitude of other respiratory stimuli can be estimated by determining the $PaCO_2$ at which apnea occurs. Apneic points below 30 to 38 mm. Hg (mean 35 mm.) imply respiratory drives superimposed on or augmenting normal stimulation of CO_2 [28].

Carbon dioxide thresholds were determined by regression in twelve subjects with CSR. Five of these subjects also had CO_2 thresholds measured directly while breathing O_2. Thresholds were measured in control subjects with congestive heart failure, unilateral and bilateral strokes, and in normal subjects.

Figure 5 presents the results. Patients with CSR had thresholds ranging between 37.5 and 25 mm. Hg $PaCO_2$ (mean 31.5 mm. Hg). Calculated thresholds and observed apneic points agreed within 2 mm. Hg. The mean threshold was similar to that found in congestive heart failure (mean 32 mm. Hg $PaCO_2$) but it was higher than that found in subjects with strokes who were breathing regularly. These data indicate that non-chemoceptive respiratory stimuli are no greater in periodic breathing than in congestive heart failure with regular breathing. The data are insufficient to determine whether the threshold differences in the neurologic patients with regular breathing were significant in preventing hyperventilation apnea.

Sensitivity to CO_2: Twelve patients with CSR were tested for their ventilatory response to graded $PaCO_2$ increases. Comparative and control studies were performed in four patients whose breathing was regular but who had bilateral cerebral infarction. Three subjects with unilateral strokes, three subjects with congestive heart failure and four normal subjects were also studied. The data are summarized in Figure 6. Every subject with CSR showed an augmented response to increased $PaCO_2$ [29]. Thus a 10 per cent rise in $PaCO_2$ evoked an 18 L./minute increase in mean alveolar ventilation among subjects with CSR, while a 10 per cent $PaCO_2$ rise evoked only a 5 L./minute increase in mean alveolar ventilation among normal subjects [28–30]. Confirming the findings of Heyman et al. [31], patients suffering from bilateral cerebral disease, but lacking CSR also showed an augmented response to CO_2 (mean 12 L./minute per 10 per cent $PaCO_2$ rise). No subject with either congestive heart failure or unilateral stroke fell outside the normal range for sensitivity to CO_2.

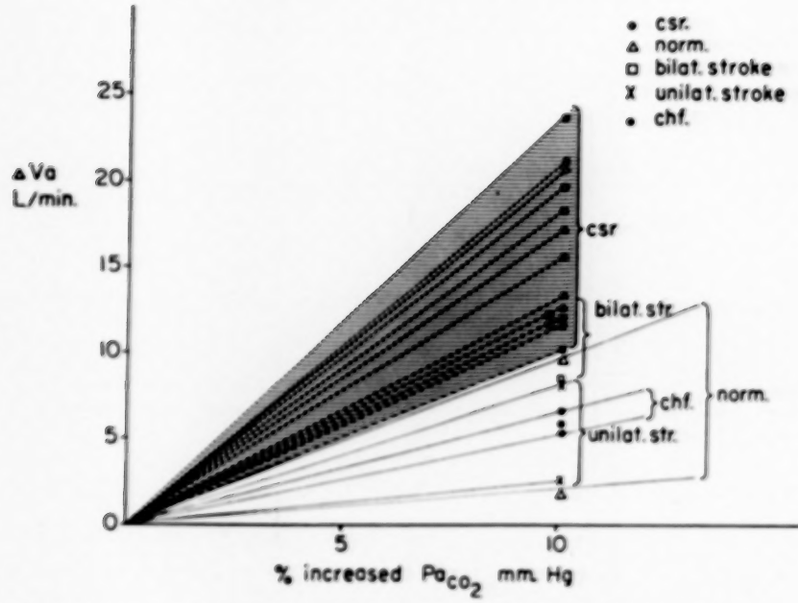
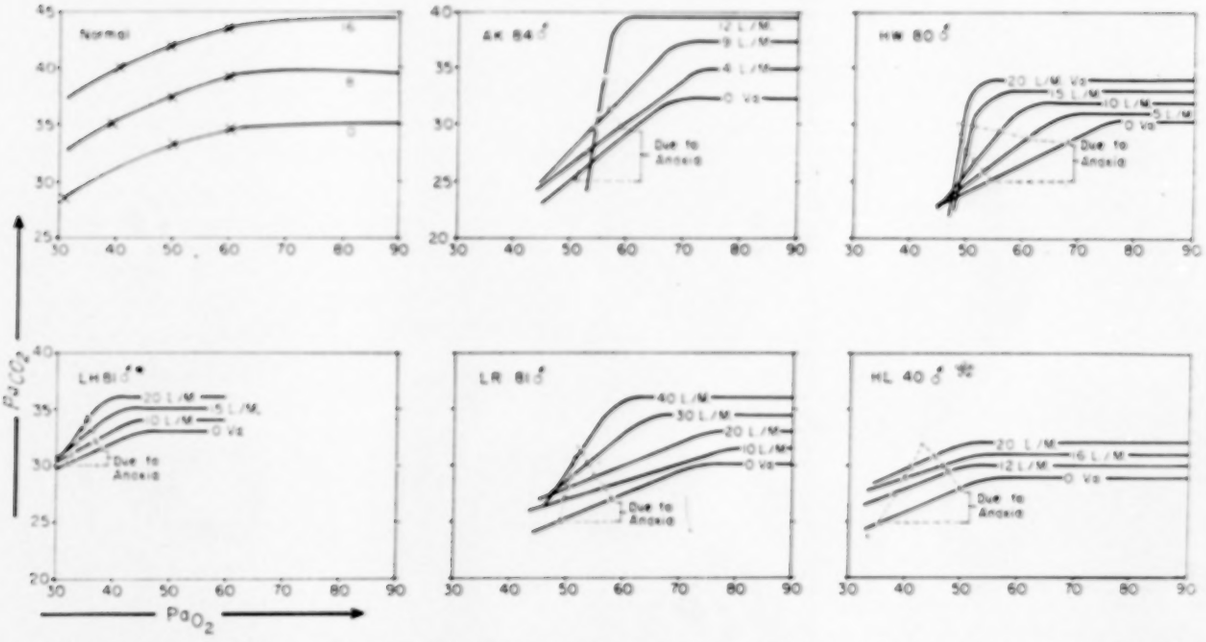


FIG. 6. Ventilatory to sensitivity CO_2 in CSR. Each line represents the response of a single patient. Brackets enclose the various clinically similar groups. Only subjects with bilateral strokes had responses which overlapped the CSR responses.



* Since patient L. H. was too ill for CO_2 sensitivity testing, only blood gas values throughout the respiratory cycle are shown.

FIG. 7. Isoventilation curves in CSR. A curve of a normal subject and five curves of patients are presented. Each heavy line passes through O_2-CO_2 coordinate points which produced equivalent minute ventilation (Va). The dotted lines connect points determined during resting ventilatory cycles. Starting with zero ventilation on the right, points move counterclockwise to maximal ventilation and return to apnea. PaO_2 falls progressively during this sequence augmenting ventilation drives. As a result, $PaCO_2$ at beginning apnea is considerably lower than $PaCO_2$ at beginning ventilation. This graphically illustrates the magnitude of anoxic drive during the latter part of the ventilatory phase.

Isoventilation curves in CSR: Isoventilation curves in five patients are diagrammed in Figure 7. Two characteristics differ in these curves when compared to normal ones [*32*]: The individual isoventilation lines in each subject were compressed together, reflecting increased ventilatory sensitivity to CO_2. Also, on the left side of the curves, in PaO_2 ranges of 45 to 60 mm Hg, individual isoventilation lines converged towards a point well below the CO_2 threshold. This ventilatory activity at reduced PCO_2 levels provides graphic evidence of the considerable chemoreceptor ventilatory drive induced by a combination of alkalosis and moderate arterial oxygen desaturation.

COMMENTS

The clinical data described here confirm the prevalence of bilateral supramedullary abnormalities of the motor system in patients with CSR. Material obtained at autopsy in these as well as most other recorded instances of CSR has substantiated the clinical observations of neurologic dysfunction, usually showing bilateral supramedullary destructive lesions in pyramidal and extrapyramidal areas extending from the cerebral hemispheres to the upper pons. Admittedly, in anoxemic patients the full extent of neurologic dysfunction may not be reflected in morphologic lesions, but neither the clinical nor the pathologic studies have provided evidence to suggest primary medullary dysfunction in patients with CSR. Although always supramedullary, the observed lesions have most often been multiple, scattered, and too different in age to identify any "center" whose loss results in periodic breathing. Anatomically, the brain lesions are much like those found with pseudobulbar palsy. Indeed, Cheyne-Stokes respiration with its excessive response to stimulation of CO_2 is reminiscent of the excessive response which occurs in other spheres (forced laughing, forced crying, stretch reflex hyperexcitability) in patients with pseudobulbar palsy.

These data confirmed the high incidence of clinically evident cardiovascular disease in patients with CSR. Pulmonary congestion was frequent and could be inferred in all cases showing arterial desaturation coincident with end ventilation. Whether the reduced oxygen tensions observed here necessarily imply a transalveolar diffusion defect is unclear. Current work with mathematical models suggests that in the absence of any morphologic pulmonary lesions apparent ventilation/perfusion defects can result from respiratory periodicity alone. Circulation times were moderately prolonged in many instances. However, neither hypoxemia nor circulatory delay was present in all cases and this alone makes it doubtful that extracerebral defects in blood flow are the common denominator to respiratory periodicity. An additional observation which inferentially makes circulatory delay unlikely as the prime cause of periodic breathing is that no patient with congestive heart failure breathed periodically unless he also demonstrated neurogenic abnormalities of the motor pathway. The frequency of CSR in hypertensive disease [*33*] may be explainable by the high incidence of subclinical cerebral vascular disease produced by hypertension [*34*].

Cheyne-Stokes breathing is a pattern of hyperventilation with intermittent posthyperventilation apnea [*21*]. Every subject showed respiratory alkalosis with maximal $PaCO_2$ coinciding with peak hyperpnea and near minimal $PaCO_2$ coinciding with beginning apnea. The cause of the hyperventilation lay in a greatly enhanced ventilatory response to suprathreshold increases in $PaCO_2$. Once the CO_2 threshold of the respiratory centers was passed in CSR subjects, ventilation per unit rise of $PaCO_2$ increased approximately three times as much as it did in normal subjects. As a result the excretion of CO_2 during hyperpnea rapidly exceeded the production of CO_2; $PaCO_2$ declined and apnea recurred.

Hyperventilation alkalosis also contributed to the respiratory stimulation which periodically lowered $PaCO_2$ below threshold. As $PaCO_2$ fell during respiratory decrescendo, arterial pH rose rapidly. Relative oxygen saturation also rose as a result of the Bohr effect [*26*]. However, arterial O_2 tension remained low or actually declined during respiratory decrescendo, prolonging chemoreceptor stimulation. Normally the chemoreceptors provide relatively little ventilatory stimulation. In the subjects with CSR, however, isoventilation curves converged to the left, close to the point where anoxemia is the only ventilatory stimulus. This explains why oxygen therapy often eliminates respiratory periodicity in Cheyne-Stokes breathing. Even with alkalosis, fully saturated arterial blood does not stimulate carotid body chemoreceptors and $PaCO_2$ never falls below threshold. (Presumably, this removal of carotid body stimulation also explains why oxygen therapy often corrects the intermittent

A-V block and bradycardia which sometimes accompanies the decrescendo phase of respiratory periodicity [*35–36*].

Although abnormalities in sensitivity to CO_2, and the closely related depression of oxygen tensions by alkalosis explain much of the pathogenesis of periodic breathing, they fail to clarify all aspects of the problem. Increased sensitivity to CO_2 is found in subjects with bilateral disease of the descending motor pathways who lack periodic breathing. Also, the increased sensitivity to CO_2 fails to change when periodic breathing is ameliorated in some patients by treating heart failure, or as alertness returns in others during recovery from acute cerebral insults. Limited data are presented herein which suggests that thresholds of CO_2 are higher in subjects with CSR than in subjects with comparable neurologic damage who lack respiratory periodicity. Also sensitivity to CO_2 was greater in subjects who breathed periodically. Whether or not these differences in threshold and sensitivity are interrelated in altering respiratory periodicity requires more study.

The observation that bilateral lesions of the descending motor pathway augment sensitivity to CO_2 in the respiratory centers has considerable theoretical interest. von Euler and Soderberg [*37*] and Comroe [*38*] have demonstrated that medullary respiratory neurones which respond to increased CO_2 tensions are separate from medullary respiratory neurones which respond to reflex stimulation. There is much evidence that increased peripheral stimulation [*37*] and, perhaps, some forms of central neurogenic stimulation [*21*] act selectively upon reflex-sensitive medullary neurones to lower ventilatory thresholds without significantly altering ventilatory CO_2 sensitivity. The present evidence, as well as that previously presented by Heyman et al. [*31*], points to an additional, entirely separate central mechanism normally exerting inhibitory effects on CO_2-sensitive medullary nerve cells. When interrupted, this central mechanism permits selective hyperactivity of CO_2-sensitive respiratory neurones, but fails to excite significantly reflex sensitive cells so that ventilatory threshold is not greatly lowered. In this regard, Cheyne-Stokes respiration with its involuntary hypersensitivity to CO_2 which often cannot be overcome by willed effort [*19*] is essentially the reciprocal of primary medullary respiratory failure in which the ability to breathe by willed effort is preserved despite marked impairment of both intrinsic sensitivity to CO_2 and respiratory autorhythmicity [*39*].

SUMMARY

1. Clinical and physiologic studies were performed in twenty-eight patients with Cheyne-Stokes respiration (CSR). Five of the twenty-eight were examined postmortem. Control studies were performed in the following groups showing regular respiration: normal subjects, patients with congestive heart failure, and patients with unilateral and bilateral cerebral vascular disease.

2. Neurologically, every subject with CSR exhibited signs of bilateral descending motor system dysfunction at supramedullary levels. Cardiac abnormalities and circulatory congestion, although frequent, were undetectable in five cases.

3. Every subject with CSR had hyperventilation and respiratory alkalosis. Peak ventilation coincided with maximal $PaCO_2$, and apnea coincided with $PaCO_2$ levels considerably below the ventilatory threshold.

4. Every subject with CSR had an increased respiratory sensitivity to CO_2, the mean ventilatory CO_2 response being approximately three times the normal. This increased sensitivity, which resulted from bilateral supramedullary brain dysfunction, was the principal cause of hyperpnea. Ventilation in CSR was also augmented by reduced oxygen tensions, resulting from moderate arterial oxygen desaturation. As a result, during late respiratory decrescendo, anoxemia continued to drive ventilation despite $PaCO_2$ levels considerably below the respiratory-stimulating threshold.

5. Periodic breathing is a pattern of neurogenic hyperpnea in which intense hyperventilation alternates with posthyperventilation apnea. Extracerebral abnormalities, although they may augment ventilatory periodicity, are not the primary cause of Cheyne-Stokes respiration.

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Cerebral Circulation and Function in Cheyne-Stokes Respiration*

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CHEYNE-STOKES respiration occurs in a variety of illnesses, particularly in cardiovascular and central nervous system diseases. Although the basic mechanism initiating this form of periodic breathing is not known, phasic changes in blood gases and prolongation of the circulation time are generally recognized to be important pathogenetic factors [*1–4*]. Hyperpnea follows the decrease in arterial oxygen saturation and increase in carbon dioxide tension observed late in the apneic cycle of Cheyne-Stokes respiration. With a delay in circulation time, which is often present due to underlying cardiac failure, the maximal changes in blood gases produced in apnea do not affect the respiratory center until the mid-portion of hyperpnea. Consequently, the hyperpneic phase is prolonged and overcorrects the derangement in arterial oxygen saturation and carbon dioxide tension. This, in turn, influences the regulation of respiration and the duration of apnea in the succeeding period, resulting in moderately severe alteration of blood gases. Thus, the cycles of apnea and hyperpnea are perpetuated and associated with swings in arterial oxygen and carbon dioxide values.

Early descriptions of Cheyne-Stokes breathing called attention to the fact that phasic changes in respiration are associated with cyclic alterations in circulatory and central nervous system functions [*5,6*]. These include fluctuations in consciousness with drowsiness or stupor in apnea and confused agitation in hyperpnea. Constricted pupils, conjugate deviation of the eyes, hyporeflexia and abnormal plantar responses have also been observed in apnea [*7,8*]. Phasic changes in the electroencephalogram have likewise been reported [*9*]. Periodic alterations have been observed in the pulse [*10–12*], blood pressure [*13*] and cerebrospinal fluid pressure [*14*].

Although these cyclic changes in cerebral and circulatory function are observed frequently in periodic breathing, their relationship to the cerebral blood flow has not been investigated. This report presents our observations on the phasic alterations of cerebral circulation in Cheyne-Stokes respiration and correlates those alterations with changes in blood gases, electroencephalographic activity and state of consciousness.

METHODS

Observations were made on seventeen patients. Fifteen of these had cardiovascular disease, cerebrovascular disorders or both; the remaining two had evidence of the obesity cardiorespiratory syndrome. (Table 1.) All the patients were men; the majority were between fifty-five and seventy years old. Most of them were seriously ill with clinical evidence of hemiplegia, congestive heart failure or uremia. Many were in a semi-comatose state and could not be aroused for long periods of time. Nine patients died during hospitalization within days or weeks after completion of the study. Repeated observations were made on seven patients.

The study was usually performed with the patient in the semi-reclining position. The introduction of indwelling arterial and venous needles and other preparations for the study occasionally abolished the Cheyne-Stokes respiration. In such instances 5 to 10 mg. of morphine was given intravenously to restore the periodic respiration. Apnea followed by the typical respiratory pattern of Cheyne-Stokes breathing was reinstituted in some subjects by a short period of voluntary hyperventilation. Electroencephalograph records were obtained from the scalp using silver chloride disc electrodes cemented with collodion. The electrodes were placed on standard anterio-

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TABLE I

CLINICAL AND ELECTROENCEPHALOGRAPHIC DATA OF PATIENTS WITH CHEYNE-STOKES RESPIRATION

Patient and Age (yr.)	Diagnosis	Abnormalities Revealed by Electroencephalogram	Cyclic Electroencephalographic and Mental Changes	Remarks
F. F.,61	Right cerebral infarct; metastatic cancer; hypertensive vascular disease	Record revealed abnormalities with much low voltage theta activity primarily on the right	Low voltage during apnea with increase during hyperpnea; cloudy sensorium with no phasic changes	Blood pressure 200/120 mm. Hg; died three days after study
J. L.,41	Hypertensive vascular disease; uremia	Generally a flat featureless record	Increased voltage and frequency in hyperpnea; responds to commands only in this phase	Blood pressure 260/180 mm. Hg; died four days after study
E. A.,68	Heart failure; diabetes mellitus; right cerebral infarct	Generalized low voltage, slow frequency record	Definite flattening of electroencephalogram in apnea with slow alpha in hyperpnea; hypokinetic; drowsy with no phasic changes in awareness	Died five months after study; received 7 mg. morphine during study
R. P.,64	Hypertensive vascular disease; left cerebral infarct	Bilateral theta activity with higher voltage on the left	Higher amplitude during hyperpnea without change in frequency	Blood pressure 250/150 mm. Hg; received 7.5 mg. morphine during study
D. W.,67	Right cerebral infarct; heart failure	Bilateral theta activity, possibly worse on the right side	Definite phasic alterations of electroencephalogram with periodic breathing; sensorium clearer during hyperpnea (Fig. 1)	Pupils dilate in hyperpnea; died five months after study
H. B.,61	Heart failure	Generalized moderate voltage theta activity	Higher voltage in hyperpnea; restlessness in hyperpnea	Died two weeks after study; received 7.5 mg. morphine during study
J. L.,32	Obesity cardiorespiratory syndrome	Borderline normal record	Faster frequencies appear with hyperpnea (Fig. 3); drowsy but lucid with slight phasic changes in awareness	Weight 350 pounds
J. S.,63	Hypertensive vascular disease; right cerebral infarct	Moderate abnormalities with slower frequencies and higher voltage on the right	Increase in frequency and voltage in hyperpnea; no phasic changes in consciousness	Blood pressure 200/115 mm. Hg; received 10 mg. morphine during study
T. J.,68	Heart failure; left cerebral infarct	Generalized theta activity, increased voltage and slower frequencies on left	Cyclic electroencephalographic changes apparent and more obvious on the right side; more awareness in hyperpnea	Died seven months later
H. K.,59	Diabetes and mellitus; epilepsy; mental deterioration; hypertensive vascular disease	Borderline normal record with alpha activity present but poorly organized	Record shows improvement in late hyperpnea; no changes in consciousness	Blood pressure 210/110 mm. Hg; received 10 mg. morphine during study
J. T.,61	Heart failure; brain stem infarct	Normal record with slow alpha activity	During apnea slow waves predominate; slow alpha appears in mid-hyperpnea	. . .
S. W.,28	Obesity cardiorespiratory syndrome	Slow alpha activity, generalized low voltage record	Somnolence with arousal during hyperpnea	Weight 550 pounds

TABLE 1 (*Continued*)

CLINICAL AND ELECTROENCEPHALOGRAPHIC DATA OF PATIENTS WITH CHEYNE-STOKES RESPIRATION

Patient and Age (yr.)	Diagnosis	Abnormalities Revealed by Electroencephalogram	Cyclic Electroencephalographic and Mental Changes	Remarks
W. M.,69	Hypertensive vascular disease; heart failure	Moderately abnormal record	Cyclic electroencephalographic changes with increased voltage in hyperpnea and theta and slow alpha waves in apnea	Blood pressure 210/140 mm. Hg; died one and a half years after study; received 7.5 mg. morphine during study
G. W.,60	Heart failure; left cerebral infarct	Moderately abnormal record with much theta activity	Responds slowly during apnea with high voltage slow waves, particularly on the left; responds rapidly and faster frequencies appear in hyperpnea	. . .
W. C.,59	Diabetes, mellitus, right cerebral infarct	Very abnormal record with high voltage slow activity	Faster frequencies appear in mid-hyperpnea; no change in consciousness	Blood pressure 100/60 mm. Hg; died nineteen days after study
M. A.,66	Hypertensive vascular disease; right cerebral infarct	Very abnormal record with high voltage slow waves, maximal on right	No changes with respiratory cycles	Blood pressure 290/160 mm. Hg; died six months after study
C. G.,65	Hypertensive vascular disease; brain stem infarct	Normal record with symmetrical alpha	Increase in alpha amplitude during hyperpnea; poorly regulated alpha in apnea	Blood pressure 216/100 mm. Hg

posterior positions of the head. The respiratory pattern was recorded simultaneously on one channel of the electroencephalograph by means of a pneumograph. Heparinized blood samples were obtained from the brachial artery and the bulb of the internal jugular vein using manifolds of syringes attached to indwelling needles. In each subject multiple simultaneous arterial and venous blood samples were obtained during the apneic and hyperpneic phases of the respiratory cycle. The cerebral arteriovenous oxygen difference ($[A\text{-}V]O_2$), arterial blood gases, electroencephalographic pattern and state of consciousness were correlated for the periods of apnea and hyperpnea.

In certain patients continuous measurement of the spinal fluid pressure was made through a needle inserted in the lumbar subarachnoid space. Arterial blood pressure was measured through an indwelling needle in the brachial artery, and both the arterial and spinal fluid pressures were recorded simultaneously with the respiratory pattern. The circulation time was determined in each patient by injection of Evans blue dye into a vein in the antecubital fossa, using the appearance time in the brachial arterial blood as an end point. In several subjects the circulation time between the carotid artery and jugular vein was estimated during apnea and hyperpnea using the same Evans blue dye technic.

In representative cases the electroencephalogram was analyzed manually with the analysis extending over the time period during which the blood samples were drawn [*15*]. The results were expressed as per cent of the total time occupied by waves of frequencies between 1 and 14 per second. Only one channel was analyzed (usually the central-posterior area), the selection being determined by its freedom from artifact. In patients with unilateral lesions of the cerebral hemisphere, the normal side was chosen for analysis.

Oxygen content and saturation were determined for both arterial and venous blood; carbon dioxide and pH were measured with arterial blood only. The blood oxygen content and saturation were determined by the photometric method of Hickam and Frayser [*16*]. In several instances arterial, jugular venous and femoral venous blood was drawn through a Woods oximeter to follow continuously the change in oxygen saturation. The pH of whole blood was measured with a Cambridge pH meter at room temperature and corrected to 37°c. by Rosenthal's factor [*17*]. The carbon dioxide content of whole blood was determined by the method of Van Slyke and Neill [*18*], and the plasma carbon dioxide content

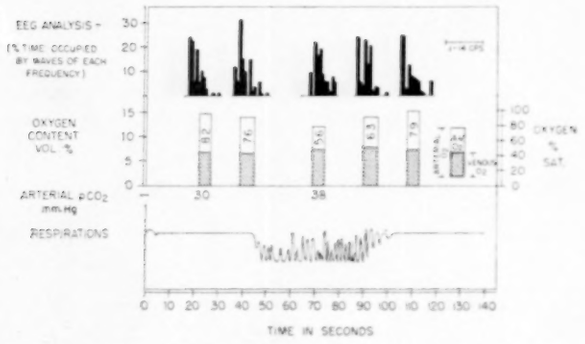

FIG. 1. Patient D. W. Example of the relationship between the changes in cerebral arteriovenous oxygen differences, arterial blood gases and electroencephalogram during one cycle of Cheyne-Stokes respiration. Width of bar for $(A\text{-}V)O_2$ indicates period of time to obtain samples.

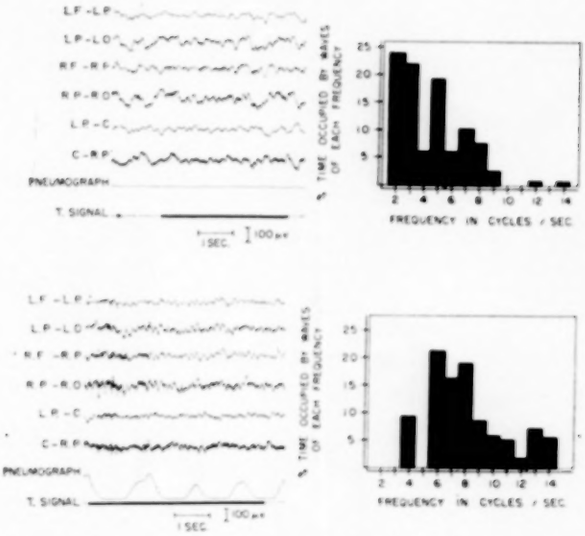

FIG. 2. Sample of detailed analysis of electroencephalogram in apnea (upper chart) and hyperpnea (lower chart).

was calculated from this value, pH, and hemoglobin using the line chart of Van Slyke and Sendroy [*19*]. Arterial carbon dioxide tension was calculated using the Henderson-Hasselbalch equation with pK of 6.11.

RESULTS

The characteristic relationship between the changes in cerebral arteriovenous oxygen difference, arterial blood gases, and the electroencephalogram during one cycle of Cheyne-Stokes breathing is shown in Figure 1. In this patient (D. W.) the cerebral $(A\text{-}V)O_2$ fell from 8.24 volume per cent during mid-apnea to 5.63 volume per cent in mid-hyperpnea. The arterial oxygen saturation was highest (95.2 per cent) and carbon dioxide tension lowest (30 mm. Hg) in mid-apnea. Conversely, in mid-hyperpnea the arterial oxygen saturation was lowest (82.5 per cent) and the carbon dioxide tension highest (38 mm. Hg). A detailed analysis of the electroencephalogram in apnea revealed that 70 per cent of the time was occupied by waves in the range of 2 to 5 per second. (Fig. 2.) This contrasts with the analysis during hyperpnea in which 80 per cent of the time was occupied by waves with frequencies ranging from 5 to 10 per second. A similar relationship for cerebral $(A\text{-}V)O_2$, blood gas and electroencephalographic changes is represented by a patient with Cheyne-Stokes respiration associated with the obesity cardiorespiratory syndrome. (Fig. 3.) In this subject (J. L.) the phases of the respiratory cycle were considerably shorter than those observed in patients with heart failure or brain damage.

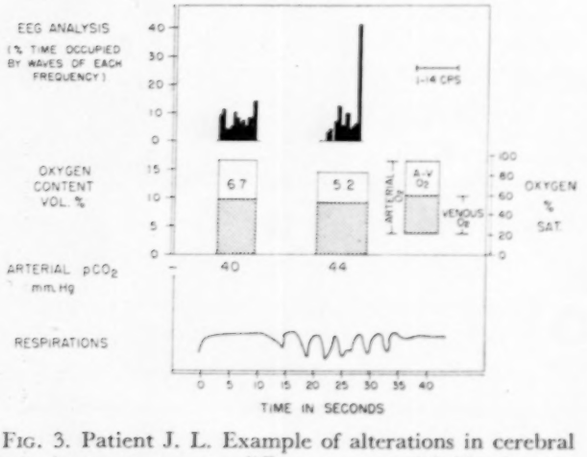

FIG. 3. Patient J. L. Example of alterations in cerebral arteriovenous oxygen differences, arterial blood gases and electroencephalogram with Cheyne-Stokes respiration in patient with obesity cardiorespiratory syndrome. Width of bar indicates period of time for obtaining samples.

The alterations in arterial blood gases, cerebral $(A\text{-}V)O_2$, circulation time and duration of respiratory cycle observed during apnea and hyperpnea are shown in Table II. The duration of the periods of apnea and hyperpnea ranged from five to seventy seconds. In general, the patients with the most prolonged circulation time had the longest periods of apnea and hyperpnea. The range of cerebral $(A\text{-}V)O_2$ in our patients was quite variable and many of them had values greater than 6 volume per cent or the mean value for young control subjects. In every instance there was a fall in the cerebral $(A\text{-}V)O_2$ during hyperpnea at which time the oxygen saturation was lowest and carbon dioxide ten-

TABLE II

ARTERIAL BLOOD GASES AND CEREBRAL ARTERIOVENOUS OXYGEN DIFFERENCES IN CHEYNE-STOKES RESPIRATION

Patient	Date	Arterial O_2 % Saturation		Arterial pCO_2 (mm. Hg)		Cerebral $(A\text{-}V)O_2$ (vol. %)		Duration (sec.)		
		Apnea	Hyperpnea	Apnea	Hyperpnea	Apnea	Hyperpnea	Circulation Time	Apnea	Hyperpnea
F. F.	3/19	89.6	84.9	33	33	6.51	5.60	15	9	15
J. L.	4/4	95.0	80.3	32	39	6.40	5.16	45	23	34
E. A.	4/6	89.3	80.0	33	37	9.90	7.92	35	15	36
	4/11	95.2	90.8	28	37	8.28	7.15	30	10	30
R. P.	3/30	98.6	97.1	36	40	11.70	11.00	20	26	20
D. W.	9/20	93.8	79.8	28	33	10.03	7.47	42	45	60
	10/19	95.2	82.5	30	38	8.24	5.63	40	48	62
H. B.	12/2	90.8	88.8	23	26	13.28	12.66	50	15	30
	12/13	86.8	84.0	35	40	5.72	4.89	30	15	25
J. L.	9/1	99.7	93.9	40	44	7.06	5.30	8	5	15
J. S.	7/22	96.8	95.2	43	49	7.79	4.50	20	10	14
	7/28	95.0	94.0	47	50	7.58	6.32	20	10	14
	9/30	98.8	94.8	...	...	10.57	7.52	25	30	20
	10/6	91.3	88.7	40	44	8.40	7.43	20	15	20
T. J.	7/15	98.7	88.3	34	42	8.71	5.16	35	20	26
	10/21	95.5	89.3	24	33	8.48	6.14	35	20	26
H. K.	5/12	91.8	91.6	53	54	8.07	6.25	15	15	30
	5/19	95.3	93.5	56	56	5.78	3.80	15	14	14
J. T.	8/8	87.5	81.4	...	...	7.00	5.00	32	20	30
S. W.	9/16	93.1	82.3	54	62	6.88	5.10	16	15	20
W. M.	4/25	97.3	90.4	47	50	5.92	5.40	15	16	28
G. W.	5/16	95.5	91.9	32	34	13.21	9.90	60	70	60
	5/23	94.6	84.2	28	40	12.96	8.33	60	54	56
W. C.	5/28	93.5	95.3	27	32	3.87	2.90	25	18	20
M. A.	7/2	93.1	91.1	28	38	8.40	6.97	20	20	16
C. G.	7/9	92.9	89.8	40	41	11.83	9.06	23	18	40

sion highest. Only one patient (H. K.) showed a change in cerebral $(A\text{-}V)O_2$ without a corresponding change in blood gases as seen in the other subjects.

Marked hypoxemia was apparently not an important factor in the production of the cerebral dysfunction in these patients, since only four showed a persistent reduction in oxygen saturation of less than 93 per cent throughout the apneic and hyperpneic phases of respiration. In most patients the changes in oxygen saturation ranged from 2 to 7 per cent during the periodic breathing, but several had swings as wide as 10 to 15 per cent. The changes in carbon dioxide tension were generally of smaller magnitude, ranging from 2 to 6 mm. Hg, but an occasional patient had as much as 8 to 11 mm. Hg variation. The arterial pCO_2 in our patients with Cheyne-Stokes respiration was usually low. Only four subjects (one of whom had the obesity cardiorespiratory syndrome) had an average pCO_2 level greater than 43 mm. Hg. During hyperpnea all but two patients showed a rise in carbon dioxide tension.

Continuous measurements of the arterial and jugular blood oxygen saturation revealed that narrowing of cerebral $(A\text{-}V)O_2$ first appeared in late apnea and reached its maximum in mid- or late hyperpnea. (Fig. 4.) The decrease in $(A\text{-}V)O_2$ was caused by both a fall in arterial oxygen saturation and a rise in venous oxygen saturation. In contrast, studies of the arterial and femoral venous oxygen difference in this patient did not show a rise in venous oxygen saturation during hyperpnea. The narrowing of the $(A\text{-}V)O_2$ across the leg during hyperpnea, therefore, was not as marked as that across the brain.

The changes in the cerebral circulation as manifested by the cerebral $(A\text{-}V)O_2$ were re-

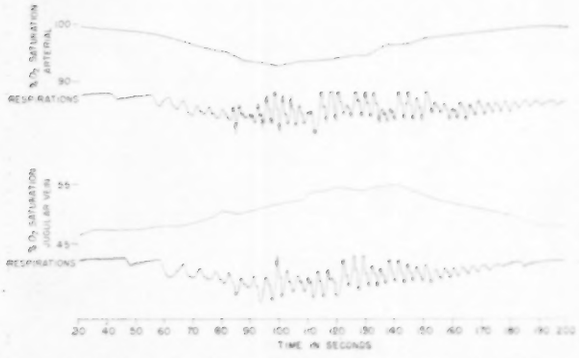

FIG. 4. Demonstration of the fall in arterial oxygen saturation and rise in jugular venous oxygen saturation which occurred during hyperpnea.

flected in alterations of spinal fluid pressure. As exemplified in Figure 5, the spinal fluid pressure rose from 180 mm. H_2O during apnea to 260 mm. H_2O during hyperpnea. Associated with this was a rise in mean arterial pressure from 70 mm. Hg in apnea to 85 mm. Hg in hyperpnea. Confirmatory evidence of an increased cerebral circulation during hyperpnea was obtained in a limited number of determinations of the carotid artery-jugular vein circulation time with the Evans blue dye method. For example, a circulation time of fourteen seconds was observed when the dye was injected at the beginning of hyperpnea, and seventeen seconds when it was injected early in apnea. It would appear, therefore, that the narrowed cerebral $(A\text{-}V)O_2$ during hyperpnea reflects an increase in cerebral circulation and not a change in cerebral oxygen uptake, since it was associated with an increase in spinal fluid pressure and a faster circulation time across the brain.

The cyclic changes in the electroencephalogram during Cheyne-Stokes respiration consisted characteristically of a shift from moderate voltage slow waves during apnea to faster frequencies in hyperpnea. (Table I.) In some patients, however, the electrical activity changed from a flat featureless record in apnea to higher voltage theta waves in hyperpnea. Such records were usually found in stuporous patients and were considered to represent evidence of improvement in the electroencephalogram during the hyperpneic phase. In other subjects irregular alpha rhythm seen in apnea became more regular and better formed in hyperpnea. The electroencephalograms showed fewer abnormalities during hyperpnea in twelve of fifteen patients in whom technically satisfactory records were obtained. Three patients (W. C., M. A. and R. P.) who had very abnormal electroencephalograms showed little or no changes in electrical pattern during the respiratory cycles. In patients with cerebral infarction, cyclic changes were less apparent over the affected cerebral hemisphere. The changes in the electroencephalogram tended to lag behind the alterations in respiration with most of the slow waves appearing in mid- to late apnea and the fast electrical activity in mid- to late hyperpnea.

In the ten patients in whom the state of consciousness was carefully observed, five were noted to become more alert during hyperpnea. During apnea they became unresponsive and were unable to answer questions or follow simple instructions. With the onset of respiratory movements, the pupils frequently dilated and the patients became restless and agitated often repeating words and phrases they had voiced during the previous period of hyperpnea. During this time they would answer questions, follow commands and generally seemed to be more responsive. Auditory, photic and painful stimuli during apnea often failed to produce arousal or electroencephalographic changes comparable to those seen in hyperpnea.

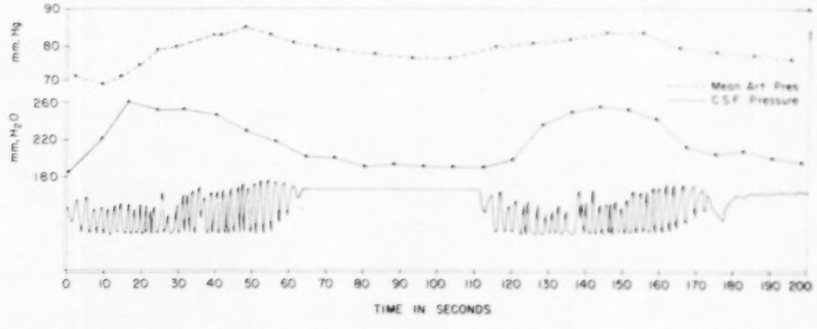

FIG. 5. Changes in spinal fluid and arterial pressures during phases of Cheyne-Stokes respiration.

COMMENTS

The results of this study indicate that the periodic breathing of Cheyne-Stokes respiration is associated with definite fluctuations in cerebral arteriovenous oxygen difference. In mid-apnea with a decreased arterial carbon dioxide tension and an increased oxygen saturation, there is widening of the cerebral arteriovenous oxygen difference. Conversely, during hyperpnea, in association with a rise in arterial carbon dioxide tension and fall in oxygen saturation, the arteriovenous oxygen difference narrows. It is postulated that the decrease in cerebral arteriovenous oxygen difference in mid-hyperpnea is an indication of an increase in cerebral blood flow. This is supported by the observation that spinal fluid pressure is increased during this phase of Cheyne-Stokes breathing. If the skull is considered as a rigid container, fluctuations in spinal fluid pressure should reflect a change in size of the cerebral vascular bed, and an increase in spinal fluid pressure would be evidence of an increase in cross sectional area of the cerebral blood vessels. In addition, our observations that the carotid artery-to-jugular vein circulation time is shortened during hyperpnea adds further support to the interpretation that the narrowed arteriovenous oxygen difference represents increased blood flow.

An alternate explanation for the narrowed arteriovenous oxygen difference during hyperpnea is that cerebral oxygen consumption is decreased. This would appear less likely in view of the improvement in the patient's mental state and electroencephalogram during this phase of Cheyne-Stokes breathing. Direct measurements of cerebral metabolism and blood flow during the cycles of periodic breathing would provide a definite answer. The indirect evidence, however, based on changes in cerebrospinal fluid pressure and circulation time suggests that narrowing of cerebral arteriovenous oxygen difference represents an increase in cerebral blood flow, and a widening of the difference represents a decrease in flow.

In practically every patient the alterations in cerebral arteriovenous oxygen difference observed during the phases of Cheyne-Stokes respiration were related to changes in arterial blood gases. It is probable that the increase in arterial oxygen saturation and decrease in carbon dioxide tension during apnea were responsible for cerebral vasoconstriction and, conversely, hypoxemia and an increase in carbon dioxide tension during hyperpnea were responsible for vasodilatation. Thus it would appear that the periodic breathing with its consequent alterations in blood gases was responsible for the observed changes in cerebral circulation.

Additional phasic events which may be related to the alterations in cerebral circulation include fluctuations in blood pressure and changes in pulse rate and cardiac rhythm [*11–13*]. Eyster [*13*] reported that in patients with increased intracranial pressure the blood pressure and pulse rate fell during apnea and rose in hyperpnea, whereas in patients with heart failure the converse was noted, i.e., an increase in pressure and pulse in apnea and a reduction in hyperpnea. This difference between the two types of illnesses was not observed in the present study. In this regard, measurements of cardiac output during the phases of Cheyne-Stokes respiration would be of interest and it is possible that the observed decrease in cerebral arteriovenous oxygen differences in hyperpnea is the result of a cyclic increase in cardiac output. Despite this possibility of an over-all increase in circulation in hyperpnea, our studies have shown that the blood flow in the legs, at least, does not participate to the same degree as that of the brain.

It is noteworthy that improvement in the electroencephalogram and a more normal state of consciousness often appeared during hyperpnea when the cerebral arteriovenous oxygen difference was decreased. In general, electroencephalographic changes observed in our patients with Cheyne-Stokes respiration were compatible with the patient's state of consciousness. Subjects who were relatively alert had near normal electroencephalograms whereas those with depression of consciousness had slow high voltage electrical activity. The improvement of the electroencephalogram during hyperpnea is probably not related to changes in arterial blood gases, since a decrease in oxygen saturation would not be expected to improve cerebral function, and the increase in pCO_2 was often minimal and should not influence cortical activity.

A wide variety of neurologic phenomena have been described during the apneic and hyperpneic phases of Cheyne-Stokes respiration. These include eye signs such as nystagmus, pupillary constriction and conjugate deviation during apnea and convulsive movements and spasmodic

facial contractions in hyperpnea [8]. The findings in this study suggest that these neurologic manifestations as well as the electroencephalographic changes and alterations in consciousness are the result of altered cerebral activity related to changes in cerebral circulation. It is equally possible, however, that cerebral blood flow is not the primary factor but represents one other manifestation of the cyclical activity of the central nervous system which may be responsible for the total syndrome of Cheyne-Stokes respiration.

Some of the factors which tend to perpetuate Cheyne-Stokes respiration are reasonably well understood. This type of breathing may be dependent on circulatory delay between the lungs and the respiratory center secondary to cardiac enlargement. It may also occur without a prolonged circulation time or cardiac enlargement, presumably when fluctuation in activity of the central nervous system is a primary factor. The fact that the changes in arterial blood gases are out of phase with the periods of apnea and hyperpnea has been recognized by others particularly when emphasizing the role of prolonged circulation time in the production of a parodoxical response [2,4]. Nylin [20] has shown that with cardiac enlargement there is an increase in the residual heart blood. Consequently, blood coming from the pulmonary vein appears more slowly in the arterial side of the circulation and the rate at which a given material increase in concentration on the arterial side is extremely slow. In cardiac failure a large volume of either under or over ventilated blood may be stored in the heart. As a result, there is a prolonged ejection of blood which carries either too great or too little a stimulus to maintain a normal constant respiratory pattern. A delay in acquainting the respiratory center with the effects of ventilation on the pulmonary blood appears to be fundamental in the production of one type of Cheyne-Stokes respiration. In animal experiments, it is possible to produce Cheyne-Stokes respiration by prolongation of circulation time from the heart to the brain [4].

In addition there are at least two other variables which may influence the periodic breathing. In the lungs, following hyperpnea, the well washed residual air provides a reservoir for aerating blood coming to the lung and prevents a rapid increase in carbon dioxide tension or fall in oxygen saturation in the pulmonary venous blood during early apnea. This would have the effect of prolonging the apneic phase. In addition, it appears likely that some time is required for the carbon dioxide tension within the respiratory center to change and reflect rapid fluctuations occurring in the arterial blood. Douglas and Haldane [21] suggested that such a lag normally prevented minor changes in alveolar and arterial carbon dioxide from disturbing breathing. In Cheyne-Stokes breathing, however, the fall in carbon dioxide tension late in hyperpnea may not be appreciated by the respiratory center until some time through apnea. This may be demonstrated by the patient with a tendency for Cheyne-Stokes respiration who voluntarily hyperventilates for a short period of time and initiates the alternate periods of apnea and hyperpnea. These delays between the actual events taking place in the lung and their appreciation by the respiratory center appear to be important in perpetuating Cheyne-Stokes respirations, particularly when the circulation time is prolonged.

Other cyclic changes in the circulatory or nervous system may also be implicated in perpetuating Cheyne-Stokes respiration. For example, an increase in cerebral circulation during hyperpnea would result in a less obtunded state, increased awareness and more rapid and deep respirations. With improvement in arterial oxygen saturation and a decrease in carbon dioxide tension, cerebral vascular constriction may occur with a subsequent decrease in the blood flow. It may be argued that this results in impaired cerebral function as evidenced by the mental state, neurologic examination and electroencephalogram during apnea. At this time the patient is not stimulated to breathe until an increase in cerebral blood flow again occurs with the period of hyperpnea. This serves to indicate that a number of phasic changes in the circulation and central nervous system may contribute to the continuation of Cheyne-Stokes respiration.

Although the factors which tend to perpetuate periodic breathing seem reasonably well understood, there is still little information concerning the mechanism initiating this form of respiration. It is well recognized that Cheyne-Stokes respiration appears in patients with cardiovascular and central nervous system diseases, and that it may be observed in normal persons during natural sleep, after prolonged hyperventilation and after the ingestion of drugs which depress the central nervous system. In this regard it is of

interest that the arterial carbon dioxide tension was less than 40 mm. Hg in most of our subjects, and marked hypocapnia was present during one or both phases of periodic breathing in some. Cheyne-Stokes breathing occurs, however, in situations of alveolar hypoventilation, e.g., obesity cardiorespiratory syndrome [*22*], narcolepsy [*23*] and myotonic muscular dystrophy [*24*].

On the basis of many animal experiments, Hoff and Breckenridge [*8*] conclude that Cheyne-Stokes respiration is produced by a depression of higher cerebral centers which normally act as a suppressor influence on lower respiratory systems. Thus, the elimination of cortical suppression by sleep, use of narcotics or cerebral damage is thought to result in a release of periodic respiratory rhythms intrinsic in the brain stem. There is no doubt that other factors will also initiate periodic breathing. Various workers have attempted to differentiate separate types of Cheyne-Stokes respiration and have emphasized such factors as the prolongation of circulation time [*2*], differences in blood pressure responses in the respiratory cycle [*13*] or the presence or absence of a fluctuating expiratory resting position of the chest [*25,26*]. It is apparent, however, that any explanation of the pathogenesis of Cheyne-Stokes respiration must take into consideration the intricate interrelationships of derangements in three major areas: i.e., the circulatory, respiratory and central nervous systems.

SUMMARY

Phasic alterations of cerebral circulation were studied in seventeen patients with Cheyne-Stokes breathing associated with cardiovascular disease, cerebrovascular disease or the obesity cardiorespiratory syndrome. During the hyperpneic phase of respiration, the arterial oxygen saturation was lowest, and the carbon dioxide tension highest, at which time the cerebral arteriovenous oxygen difference was decreased. The converse changes appeared in apnea. An increase in spinal fluid pressure was noted in hyperpnea and a reduction in the circulation time across the brain was also observed. Electroencephalographic abnormalities frequently disappeared during hyperpnea along with improvement in the patient's mental function and consciousness. On the basis of these observations, it is postulated that cyclic alterations in cerebral circulation appear in Cheyne-Stokes respiration with an increased blood flow during hyperpnea and a decreased blood flow in apnea.

It appears likely that the phasic alteration in cerebral circulation is the primary factor producing fluctuations in the patient's mental state, electroencephalogram and neurologic signs. It is equally possible, however, that the varying blood flow represents one more manifestation of phasic activity in the central nervous system which may be the basic cause of the syndrome of Cheyne-Stokes respiration.

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Alveolar-Arterial Gas Tension Relationships in Acute Anterior Poliomyelitis*

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IN the course of treating patients with respiratory paralysis due to acute anterior poliomyelitis many studies of arterial blood and alveolar gas have been made in an effort to determine optimum therapy. The chief objective has usually been to determine when mechanical devices for artificial respiration should be started and whether or not these devices were producing optimum results once they were in use. In the poliomyelitis epidemic in Minneapolis in 1947 the ear oximeter was used by Elam et al. [*1*]; they found the arterial blood of their patients was often unsaturated despite what was considered adequate ventilation. In 1952, Dickinson, Wilson and Graham [*2*] found alkalosis and low CO_2 tension in the arterial blood of almost every patient with progressive respiratory paralysis whom they were about to place in a respirator. In 1952 and 1953 Lassen et al. [*3*] measured arterial blood pH and O_2 saturation in patients with acute poliomyelitis. In 1953 we initiated our studies of arterial blood gas tensions and alveolar gas tensions sampled simultaneously [*4*]. In 1954 Carroll [*5*] also measured arterial blood gas tensions serially in acute poliomyelitis. In 1955, Crane et al. found normal end tidal alveolar CO_2 levels by infrared analysis in two-thirds of their patients with acute poliomyelitis whose respiratory reserve had diminished to the point that artificial respiration was considered necessary. In 1956 Linderholm [*7*], and in 1957 Walley [*8*], confirmed our observation of alveolar-arterial P_{CO_2} differences and found that they correlated with atelectasis.

This report consists of our findings during simultaneous measurements of alveolar gas and arterial blood for both CO_2 and O_2 made during collection of expired air. It was the object of this study to make such measurements in the hope that this approach would permit more accurate definition of the derangement of intrapulmonary gas exchange resulting from severe poliomyelitis and thereby make more effective treatment possible.

METHODS

The patients studied had various degrees of respiratory muscle paralysis, or bulbar involvement, or both, due to acute anterior poliomyelitis. They were studied on the hospital wards as they were being treated in respirators or on rocking beds or breathing unaided. The results of these studies were not communicated to the physicians responsible for the treatment of the patients in order that established therapeutic measures could be better evaluated unaltered. Pharyngeal suction was stopped during the three minute collections of expired gas, and the administration of oxygen was usually discontinued ten minutes before the study so that actual lung function could be better evaluated and the necessity for extra oxygen determined.

Physicochemical instruments (Beckman) were used for alveolar and expired gas analyses: a Pauling paramagnetic analyzer for oxygen and a Liston infrared analyzer for carbon dioxide. These were assembled on a mobile cart suitable for use at the bedside. (Fig. 1.) This cart was especially important because it facilitated the study of patients requiring a respirator who were too ill to be taken to a laboratory. Samples of arterial blood, however, were taken to a laboratory where the partial pressures of oxygen (P_{O_2}) and carbon dioxide (P_{CO_2}) were determined by the Riley bubble method [*9*].

The procedure used consisted of the following:

(1) The patient was permitted to breathe a known concentration of oxygen for a period of five to fifteen minutes until the concentration of alveolar O_2 and CO_2 were constant, indicating a steady state of gas exchange existed. Most often the patients breathed room air, but occasionally 100 per cent O_2 was administered. Lower concentrations of O_2 were not administered because of the critical condition of many of the patients.

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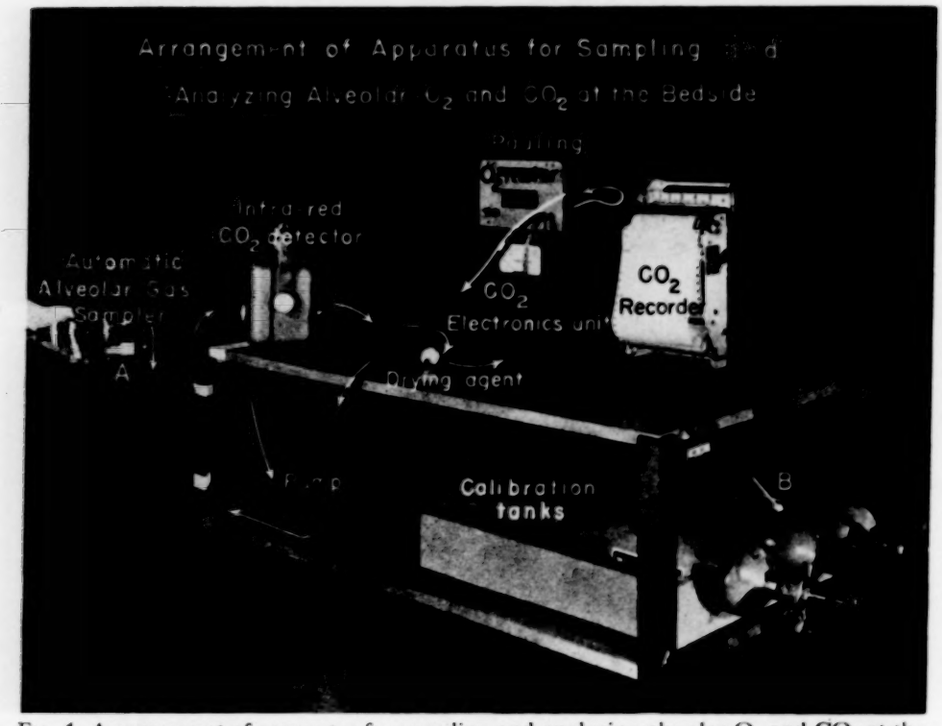

FIG. 1. Arrangement of apparatus for sampling and analyzing alveolar O_2 and CO_2 at the bedside.

(2) Local anesthesia was produced over the radial artery at the wrist with 0.5 to 1 cc. of 1 per cent xylocaine injected intradermally and subcutaneously, for the purpose of obtaining arterial blood samples.

(3) The gas analyzers were calibrated using tanks containing O_2 and CO_2 in known concentrations. These were determined by repeated micro-Scholander analyses [*10*].

(4) Alveolar gas was sampled by means of an automatic end tidal sampler [*11*] attached to a mouthpiece or tracheotomy tube, depending on the route of ventilation being used by the patient. (Fig. 2.) Samples were drawn through the O_2 and CO_2 analyzers, arranged in series, by means of a small diaphragm pump at a rate of 85 to 150 cc. per minute. Thus end tidal alveolar CO_2 and O_2 concentrations could be monitored continuously. If the rate of sampling from the balloon (flow to pump) exceeded the rate of delivery to it (respiratory frequency × balloon volume) a slight drop of carbon dioxide concentration was noted after each breath on the tracing of the infrared analyzer. This drop was caused by dead space gas contaminating the end tidal alveolar gas sampling system.

In order to minimize the possibility of dead space contamination of alveolar gas samples, additional studies were performed using direct sampling of alveolar gas from the expired air stream at the nose, mouth, or tracheotomy tube by the open method described by one of us [*12*]. Although this prevented analysis for alveolar O_2 with the Pauling type of instrument, with its slower response time, it permitted analysis of smaller alveolar gas samples for CO_2 and did not impose additional dead space or the resistance of valves on the patient.

(5) Arterial blood was sampled by means of a No. 20 short-beveled needle in the radial artery, and was collected in a 10 cc. syringe. The syringe was prepared by coating the walls and filling the dead space with a solution of concentrated heparin (10 mg./cc.) saturated with sodium fluoride. The heparin served to seal and lubricate the syringe for anerobic sampling as well as to prevent clotting of the blood; the fluoride inhibited further respiration of the red cells. Care was taken to prevent bubbles from entering the syringe by letting the pressure of arterial blood fill the syringe whenever possible.

(6) When arterial blood began to fill the syringe, stopcocks were turned so as to begin a three minute collection of mixed expired air in a Douglas bag. The fraction of end tidal alveolar gas drawn through the analyzers in the side circuit was returned to the bulk of the expired air in the Douglas bag continuously by a pump.

(7) After the arterial blood had filled the syringe, it was immediately capped, shaken vigorously and placed in an ice bath while being transported to the laboratory. The needle was removed from the artery and the puncture site compressed for five minutes.

(8) An aliquot of mixed expired gas was analyzed for CO_2 and O_2 concentrations by passage through the gas analyzers at 150 cc. per minute for three minutes.

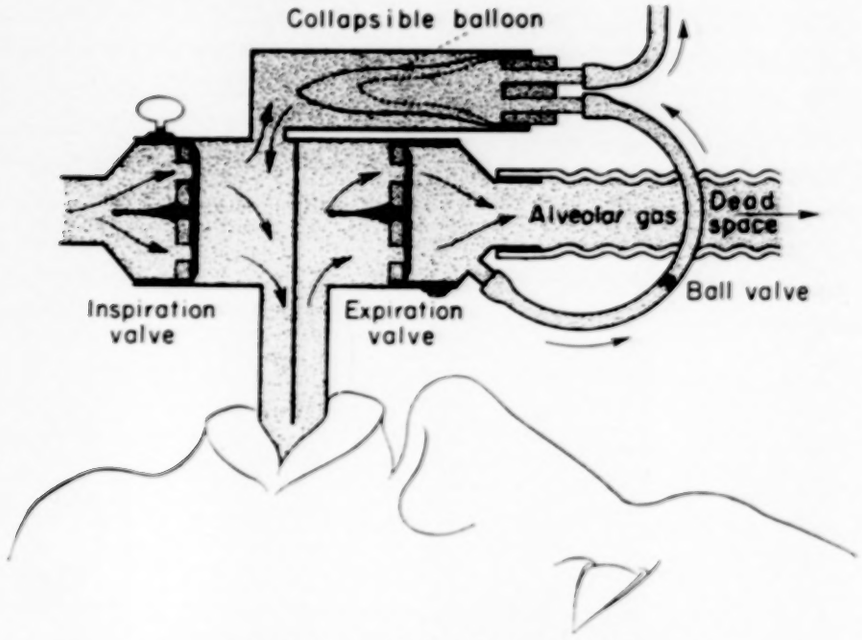

FIG. 2. Automatic alveolar gas sampler.

(9) The gas analyzers were again calibrated.

(10) The expired air volume was measured in a Tissot spirometer and corrected to *body* temperature, pressure, saturated (BTPS).

With the data obtained by this procedure the following calculations were carried out:

The rate of carbon dioxide production was calculated as the product of the volume of expired air and the concentration of carbon dioxide in the expired air:

$$\dot{V}_{CO_2} = \dot{V}_E \times F_{E_{CO_2}}$$

The rate of oxygen consumption was calculated by the following formula, correcting for the respiratory exchange ratio:

$$\dot{V}_{O_2} = \dot{V}_E \times \left[\frac{100 - (F_{E_{CO_2}} + F_{E_{O_2}})}{79} \times 20.93\right] - (\dot{V}_E \times F_{E_{O_2}})$$

The respiratory exchange ratio (R_E), representing tissue R.Q. only in a true "steady state," could then be calculated as:

$$R_E = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

The "effective" alveolar P_{O_2} was then derived geometrically from the alveolar gas tension diagram of Rahn and Fenn [*13*], or calculated using the formula:

$$P_{A_{O_2}}{}^e = P_{I_{O_2}} + \left[\frac{(P_{a_{CO_2}})(F_{I_{O_2}})(1 - R_E)}{R_E}\right] - \left[\frac{P_{a_{CO_2}}}{R_E}\right]$$

The tidal volume was derived from the mixed expired volume ($\dot{V}_E$) as:

$$V_T = \frac{\dot{V}_E}{f}$$

where *f* represents the frequency of respiration.

The body weight in pounds was taken as a rough estimate of the "normal" anatomic respiratory dead space in cubic centimeters [*14*]. Calculations of actual anatomic dead space were carried out as follows:

$$V_{D\,anatomic} = V_T\left[\frac{P_{E_{CO_2}} - P_{A_{CO_2}}}{P_{I_{CO_2}} - P_{A_{CO_2}}}\right]$$

and physiological dead space as follows:

$$V_{D\,physiologic} = V_T \times \left[\frac{P_{E_{CO_2}} - P_{a_{CO_2}}}{P_{I_{CO_2}} - P_{a_{CO_2}}}\right]$$

where $P_{A_{CO_2}}$ represents the partial pressure of end tidal alveolar carbon dioxide and $P_{a_{CO_2}}$ represents the partial pressure of arterial carbon dioxide.

RESULTS

The alveolar-arterial gas tension relationships in normal subjects and patients with non-paralytic poliomyelitis are compared with those

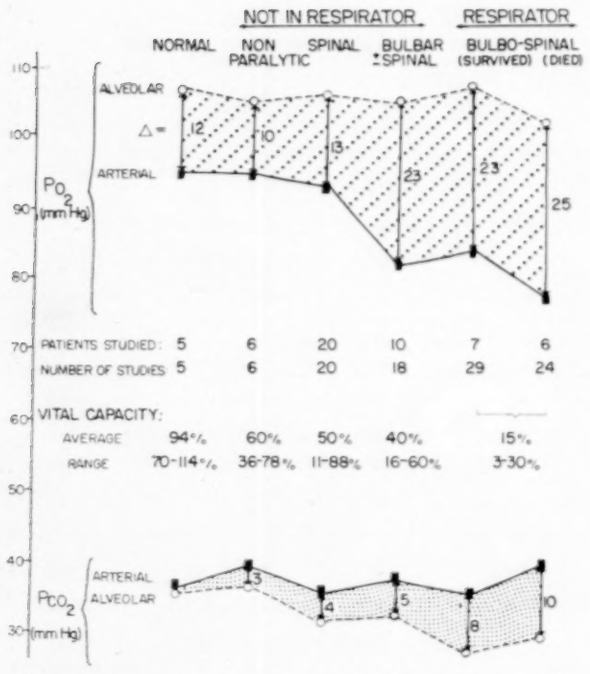

FIG. 3. Average alveolar-arterial gas tension relationships in acute anterior poliomyelitis at different stages of respiratory paralysis or bulbar involvement.

of patients with paralytic spinal, bulbar or bulbospinal poliomyelitis in Figure 3. It will be noted that the alveolar-arterial oxygen difference, or "A-a gradient," does not increase significantly until there is difficulty in swallowing, in the bulbar group, or the vital capacity is reduced to an average of 40 per cent of the expected normal value. Respiratory equipment was not used in the milder cases but was reserved for those whose vital capacity had fallen below 20 per cent of normal. Most of the bulbospinal group were receiving mechanical respiratory assistance. Despite this a number in this latter group died and, as a group, presented the largest A-a gradients for O_2 and CO_2 within a day or two prior to death. The difference between end tidal alveolar CO_2 and arterial CO_2 did not exceed the standard error inherent in the Riley bubble method (± 2 mm. Hg) unless there was bulbar involvement.

This summary of group averages cannot give a complete picture of the wide distribution of gas tensions involved. Therefore in Figure 4A the data of normal subjects, non-paralytic patients and paralytic spinal patients are presented on an $O_2 - CO_2$ diagram. The increasing area covered by the points as the disease progresses indicates the broad range of ventilatory states which may

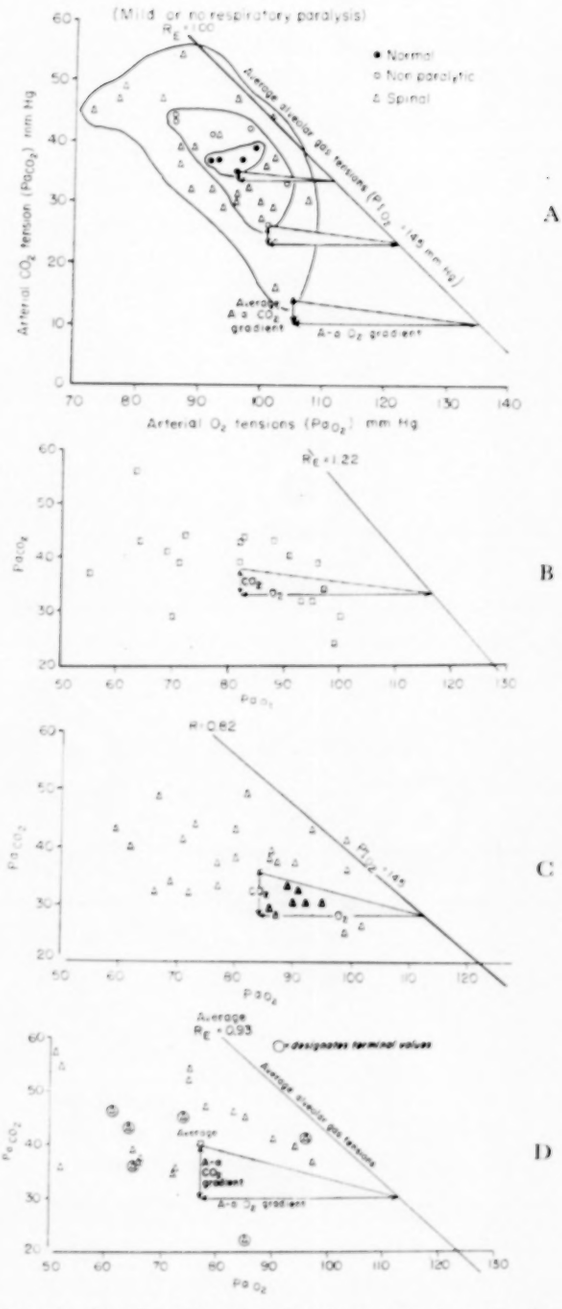

FIG. 4. Distribution of arterial gas tensions in four groups of patients. A, mild or no respiratory paralysis; B, bulbar; C, patients with bulbospinal poliomyelitis that survived; D, fatalities due to bulbospinal poliomyelitis. The average respiratory exchange ratio (R_E) is designated for each group of patients for the purpose of presenting the average A-a CO_2 and O_2 difference in the shaded areas. The individual symbols represent arterial gas tensions.

develop, for example, among patients with pure spinal disease underventilation sufficient to permit CO_2 accumulation to an arterial tension

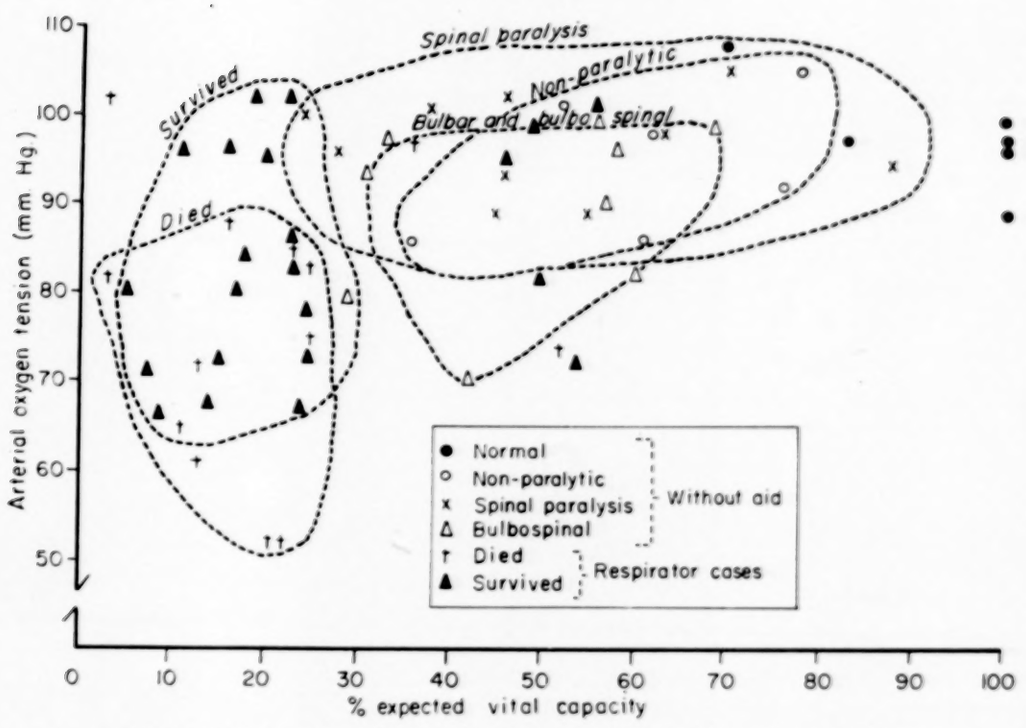

FIG. 5. Relation of arterial oxygen tension to vital capacity and prognosis.

of 54 mm. Hg and overventilation sufficient to "blow off" CO_2 to an arterial tension of 14 mm. Hg. A concept of the "gradients" involved is illustrated by relating the lowest P_{CO_2} point in each group to the respiratory exchange ratio line of 1, representing the average of these subjects. An inspired O_2 tension in the trachea of 145 mm. Hg, the average during these studies, is used as the intercept for this "R_E line" on the x-axis. It is apparent that the O_2 and CO_2 gradients tend to increase as the disease becomes worse. Figure 4D shows the distribution of the most severe cases with the average gradients drawn between the point representing mean arterial gas tensions and the mean "R_E line" of 0.93, representing the average alveolar gas. Of the six patients with terminal determinations, four had lower O_2 tensions than the average of this group. The distribution of less abnormal arterial gas tensions in the less severe cases with bulbospinal and pure bulbar involvement is shown in Figures 4B and 4C.

Arterial hypoxemia did not correlate very well, however, with the degree of respiratory paralysis. (Fig. 5.) Although patients with mild, non-paralytic poliomyelitis had arterial oxygen tensions ranging from 86 to 105 mm. Hg, the patients requiring respirators who died had values ranging from 52 to 102 mm. Hg, presenting considerable overlap between the most extreme groups. In all probability, pulmonary complications such as accumulated secretions, pneumonitis or atelectasis decrease the efficiency of intrapulmonary gas exchange and alter arterial gas tensions fully as much, if not more, than the degree of respiratory paralysis. This is most readily seen in serial studies to be discussed.

Serial studies, as presented in Figure 6, will be discussed in order to illustrate changes in alveolar-arterial gas tensions in relation to clinical events in the course of acute bulbospinal poliomyelitis. Five normal subjects are grouped on the left for comparison with a series of measurements on a polio patient on the right. The oxygen tensions are grouped above, and the carbon dioxide tensions below, so they can be read along a single scale (y-axis). In this way the effectiveness of oxygenation of the alveoli and arterial blood can be seen separately, as can the elimination of carbon dioxide from the blood to the environment. Values were determined as follows:

(1) Inspired P_{O_2}: (ambient) assumed to equal 20.93 per cent of the barometric pressure (P_B).

(2) Tracheal P_{O_2}: calculated to equal 20.93 per cent of barometric pressure less water vapor

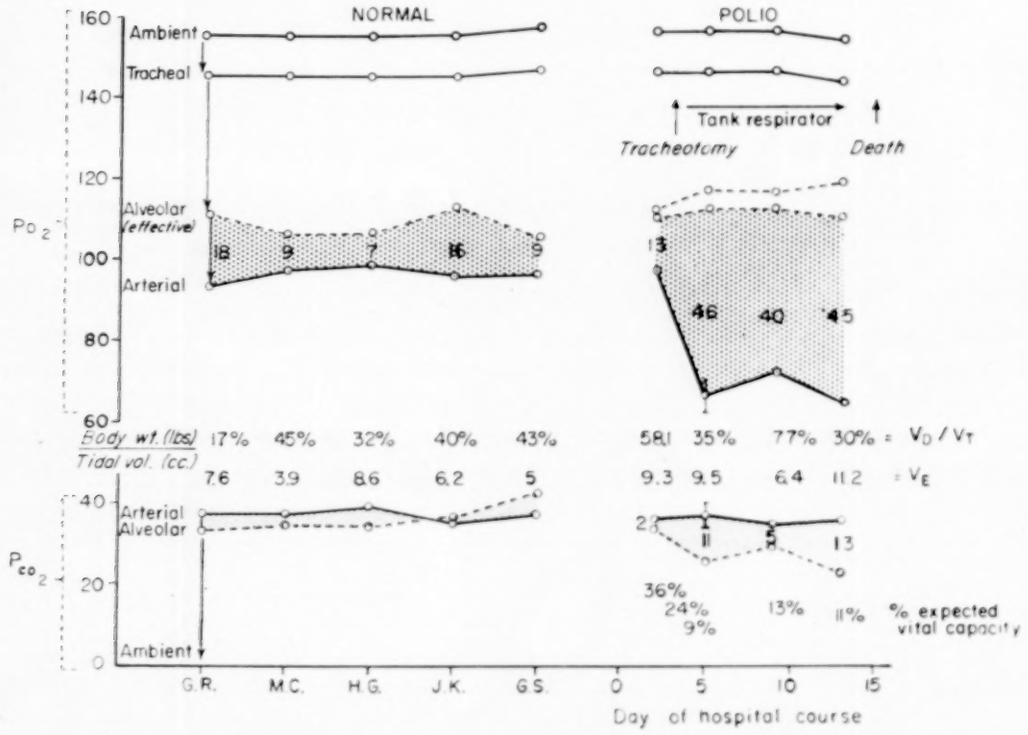

FIG. 6. Respiratory gas tensions in normal subjects and a patient with bulbospinal poliomyelitis.

pressure at body temperature (P_B −47 mm. Hg).

(3) Measured alveolar P_{O_2}: reading of the Pauling meter during the arterial blood sampling.

(4) "Effective" alveolar P_{O_2}: ($PA_{O_2}{}^e$) knowing tracheal P_{O_2}, the respiratory exchange ratio of expired air (R_E), and arterial P_{CO_2}, the $PA_{O_2}{}^e$ can be calculated or derived from the alveolar gas tension diagram [*13*].

(5) Arterial P_{O_2}: average of duplicate determinations by the Riley bubble method if they agree within ±4 mm. Hg.

(6) Arterial P_{CO_2}: average of duplicate determinations by the Riley bubble method if they agree within ±3 mm. Hg. Arterial P_{CO_2} is assumed to equal "effective" alveolar P_{CO_2}.

(7) Measured alveolar P_{CO_2}: reading of infrared analyzer on end tidal samples during arterial blood sampling.

(8) Inspired P_{CO_2}: assumed to be zero.

COMMENTS

The most striking finding of this study is that acute anterior poliomyelitis is characterized by decreasing arterial oxygen tension in the face of normal alveolar and arterial carbon dioxide tensions as the disease progresses to bulbar and respiratory muscle involvement. (Fig. 3.) This arterial hypoxemia develops before respiratory equipment is ordinarily considered necessary and often persists even after it is put into use. Arterial hypoxemia in the presence of normal arterial P_{CO_2} indicates that a defect in intrapulmonary gas exchange must exist; the hypoxemia in this case cannot be due to insufficient ventilation.

Secondly, these measurements of alveolar-arterial gas tension relationships demonstrate a consistent A-a P_{CO_2} difference which increases as the disease advances to bulbospinal involvement. Therefore it is likely, although not necessary, that whatever pathologic process caused an increased A-a O_2 difference also caused the A-a CO_2 difference to develop.

Identification of the specific defect in intrapulmonary gas exchange causing the increased A-a P_{O_2} difference requires measurement of this difference at different levels of alveolar oxygen tension. However, lowering the inspired oxygen could not be justified in these patients. Therefore, one could only surmise that a depressed arterial P_{O_2} in the presence of a normal alveolar P_{O_2} is more likely to be the result of venous admixture than a diffusion barrier.

On the other hand, identification of the defect

causing an increased A-a P_{CO_2} difference is much the same at any level of alveolar P_{CO_2} because the CO_2 dissociation curve of blood is relatively straight in the physiologic range. Furthermore, a consistent and repeatedly abnormal A-a P_{CO_2} difference (over 5 mm. Hg) lends itself to a single interpretation instead of three, as is the case for an increased A-a P_{O_2} difference. Assuming that true end tidal alveolar samples are being obtained and that reliable measurements of arterial P_{CO_2} are being made, a significant A-a P_{CO_2} difference indicates a non-uniform distribution of gas in relation to blood within the lungs. The extreme solubility of CO_2 in tissue fluids prevents the development of a true P_{CO_2} gradient across the alveolar capillary membrane of more than approximately a twenty-fifth that of the A-a P_{O_2} difference. The relatively small normal arteriovenous P_{CO_2} difference of 6 to 8 mm. Hg prevents even large arteriovenous shunts (for example, 50 per cent of cardiac output) from causing more than 3 to 4 mm. Hg A-a CO_2 difference. An increase in the average ventilation-to-perfusion ratio of the lungs, however, could theoretically produce the surprisingly large A-a CO_2 differences found in many of the cases included in the study.

In Figure 7 the maldistribution of blood and gas in the lungs of a hypothetical patient with bulbospinal polio is represented diagramatically so as to be consistent with the data found in this study. The "alveolus" on the right represents alveoli which are completely occluded by accumulated secretions which the patient is unable to cough out. As a result, the O_2 and CO_2 tensions of this trapped alveolar gas are those of the venous blood passing through the pulmonary capillary. Perfusion of this type of alveolus is assumed to continue, but at only half the normal rate. The alveolus on the left represents alveoli which are patent and ventilated twice as much as normal in order to compensate for the occluded and atelectatic areas. The alveolar CO_2 tension would, therefore, be approximately half of normal or 20 mm. Hg; the alveolar O_2 tension would rise to about 125 mm. Hg, assuming a respiratory exchange ratio of 0.82. The rate of perfusion of this type of alveolus is assumed to remain normal. The blood in any pulmonary vein draining either type of alveolus is assumed to be in equilibrium with the gas in the alveolus it has just perfused. After the confluence of all pulmonary veins in the left auricle, the mixed arterial blood is pumped to the systemic circulation where it can be sampled and compared with the mixed alveolar gas sampled at the mouth at the end of expiration. It will be noted that a considerable A-a P_{O_2} difference of 65 mm. Hg exists, indicating that 33 per cent of left heart output may consist of venous blood (that is, venous admixture), and an A-a P_{CO_2} difference of 8 mm. Hg, indicating that 40 per cent (8 mm./20 mm.) of the alveoli are equivalent to being ventilated, but not perfused (that is, alveolar dead space). Histologic examination of the lungs of patients at postmortem frequently showed a patchy distribution of atelectasis, pneumonitis and interstitial pulmonary edema, but no signs of pulmonary embolism or infarction. Therefore, the most likely cause of increased ventilation-to-perfusion ratios in respirator patients would seem to be the fact that just when alveolar ventilation is greatest, that is, when the respirator is inflating alveoli, the flow of venous blood to the right auricle is being impeded by the increased intrathoracic pressure produced by the respirator [*15*]. A second possible cause for increased ventilation-to-perfusion ratios is compensatory hyperventilation of open segments of the lungs where perfusion may be only normal. Evidence favoring this interpretation is the fact that the quantity of pulmonary ventilation was found to be normal or excessive in almost every case studied. Data to support this hypothesis can be seen in Figure 6 when the A-a CO_2 difference increased from 5 to 13 mm. Hg between the ninth and thirteenth hospital day in association

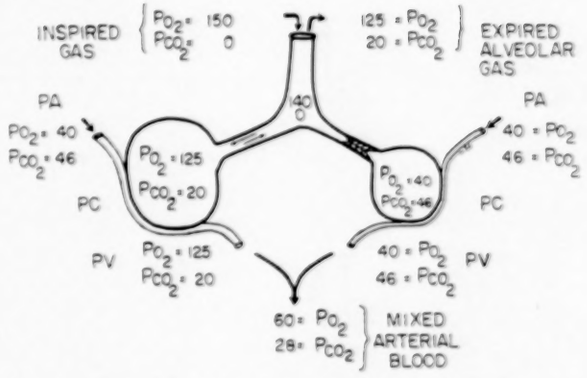

FIG. 7. Diagram of theoretical maldistribution of blood and gas in the lungs consistent with the pattern of A-a gas tension relationships observed. It is based on the following assumptions: (1) a third of pulmonary blood flow is through unventilated alveoli; (2) ventilation of the patent alveoli is twice normal; and (3) perfusion of patent alveoli is normal. PA = pulmonary artery, PC = pulmonary capillary, PV = pulmonary vein.

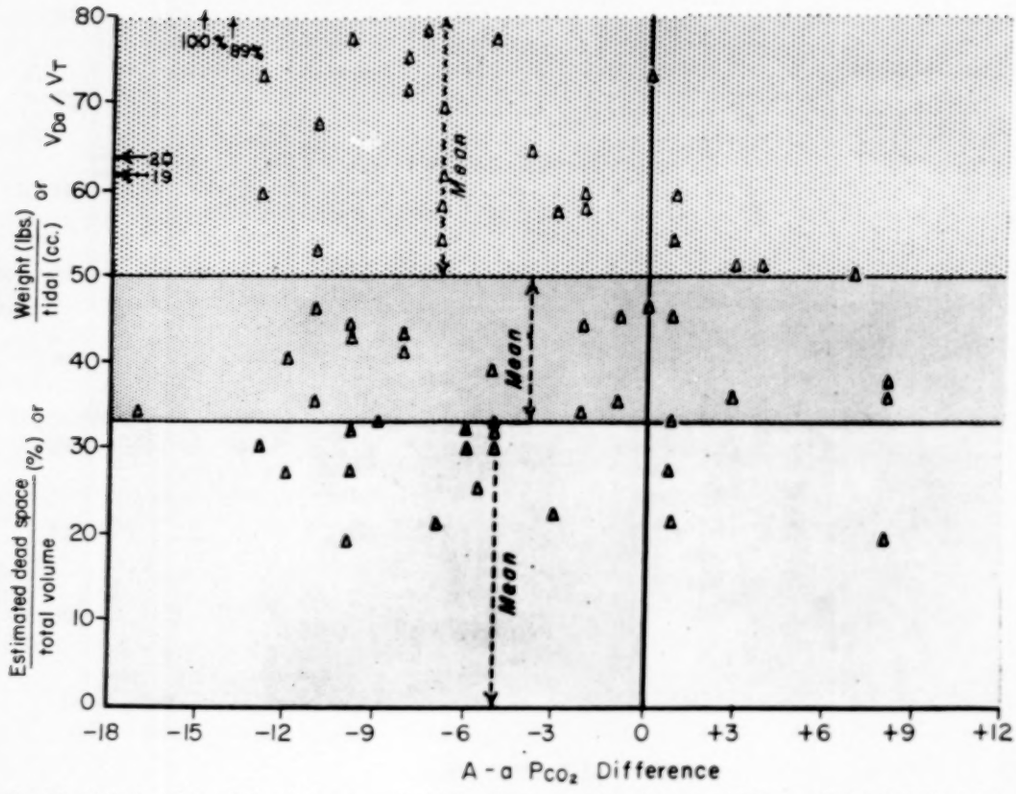

FIG. 8. Relationship of dead space and tidal volume to alveolar-arterial P_{CO_2} differences in acute poliomyelitis.

with an increase of ventilation from 6.4 to 11.2 L. per minute.

Subsequent studies presented elsewhere, on another series of patients with respiratory paralysis due to acute poliomyelitis revealed normal or accelerated nitrogen washout curves while breathing oxygen [*16*]. Normal N_2 washout curves in these patients was interpreted as indicating that ventilation of patent airways was uniformly distributed and was normal or greater than normal in volume.

To recapitulate, the following combination of findings must be explained: (1) normal distribution of inspired gas in patent airways; (2) abnormally increased ventilation-to-perfusion ratios, and (3) no histologic evidence of pulmonary vascular obstruction. The most logical explanation would seem to be that ventilation is abnormally great in relation to normal blood flow in the functioning areas of the lungs and some blood flow must continue in the atelectatic areas where no ventilation is taking place. This interpretation requires, of course, that a certain portion of pulmonary blood flow is not aerated, constituting venous admixture. This is supported by the frequent finding of abnormally increased A-a P_{O_2} differences on the flatter portion of the O_2 dissociation curve of hemoglobin when the A-a P_{CO_2} is also increased. Theoretically, only pulmonary infarction would permit such A-a P_{CO_2} differences to exist in the absence of venous admixture.

These findings are in contrast with similar studies in patients with chronic pulmonary diseases such as emphysema in whom *retarded* N_2 washout is correlated with considerable A-a CO_2 differences. Since elevated alveolar N_2 concentration after seven minutes of oxygen breathing is produced only by uneven distribution of inspired gas, and the A-a CO_2 difference is much more a function of uneven distribution of pulmonary blood flow than of inspired gas, uneven distribution of blood or gas in the lungs can be delineated nicely by use of the two tests. A full discussion of factors causing A-a CO_2 differences, and a method for calculating the percentage of alveoli which are, in effect, ventilated but not perfused, has been presented by Severinghaus [*17*].

Evidence that these A-a CO_2 differences are not due to insufficient tidal volume is summarized in Figure 8. Here the ratio of anatomic

dead space to tidal volume is plotted against the A-a CO_2 difference. Anatomic dead space is estimated on the basis of body weight [*14*]. It is apparent that there are significant CO_2 differences (5 mm. Hg) when the tidal volume is more than adequate to flush out the anatomic dead space. (V_D/V_T ratio <33 per cent.) The errors inherent in the methods of gas analysis, especially the arterial P_{CO_2} determination, is indicated by positive A-a CO_2 differences as great as 8 mm. Hg. Furthermore, blood equilibrated with gas of known CO_2 tension in a tonometer produced a range of gas-blood differences from minus 5 to plus 8, with a mean of plus 2 mm. Hg, in the course of eleven determinations. Therefore, the mean of a series of determinations on a given patient is the only significant value in this study. When V_D/V_T exceeds 50 per cent the mean is greater, as would be expected with insufficient tidal volume to wash out the tracheobronchial tree. Therefore, all values obtained from studies in which the V_D/V_T ratio exceeded 50 per cent were cast out.

The mean A-a CO_2 difference of normal subjects, non-paralytic acute patients and convalescent patients with bulbospinal poliomyelitis was found to be minus 2 mm. Hg. Since most of the convalescent polio patients studied had normal A-a CO_2 relationships, despite vital capacities in the range of 5 to 15 per cent of normal, it is concluded that an abnormal A-a CO_2 difference (>5 mm. Hg) is somewhat related to pulmonary complications in the acute stage of bulbospinal poliomyelitis and not simply to a reduction of vital capacity or the use of respiratory equipment. Apparently some excess of ventilation in relation to perfusion must exist in order to produce a significant A-a CO_2 difference.

The A-a CO_2 difference can also be related to the ratio of *physiologic* dead space to tidal volume. (Fig. 9.) The calculation of V_{D_p}/V_T has been referred to as "dead space shunting" [*18*]. The correlation indicates that as the A-a CO_2 difference increases, the "parallel" dead space of Falkow and Pappenheimer [*19*] or "alveolar" dead space of Severinghaus [*17*] increases above the simple anatomic or "series" dead space.

The patient with bulbospinal poliomyelitis, whose course is presented in Figure 6, illustrates a number of these points well, and therefore bears some discussion. As his vital capacity decreased from 36 per cent of the "normal" [*20*]

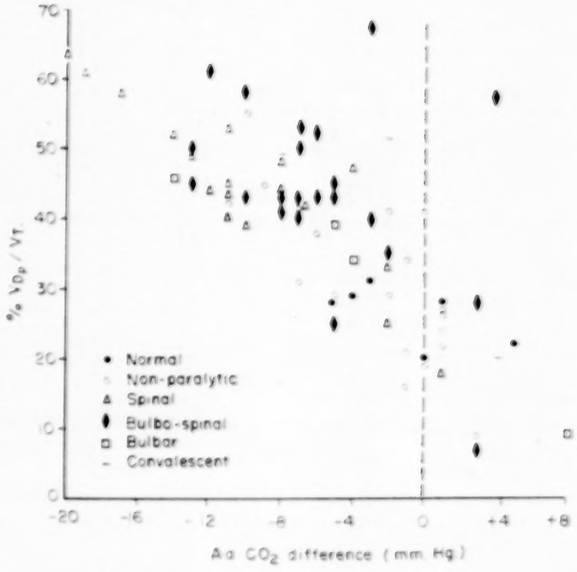

FIG. 9. Correlation of physiologic dead space with alveolar-arterial P_{CO_2} difference.

value to 9 per cent during the second and third day of hospitalization, his A-a O_2 difference was more than tripled and his A-a CO_2 difference became marked. That his arterial hypoxemia did not result from inadequate ventilation, total or alveolar, is indicated by the figures for minute ventilation ($\dot{V}_E$), alveolar P_{O_2} and alveolar P_{CO_2}. Even arterial P_{CO_2} remained normal. Therefore, some impairment of intrapulmonary gas mixing, increased diffusion barrier at the alveolar-capillary membrane or venous admixture must have existed. The production of full arterial oxygen saturation during inhalation of 100 per cent O_2 on the fourteenth hospital day indicated that venous admixture was not significant at this time. Therefore, excessive ventilation of normally perfused areas of the lungs probably contributed significantly to the increase of A-a O_2 difference as well as the A-a CO_2 difference. The fact that both the O_2 and CO_2 differences decreased on the ninth hospital day with decreased ventilation tends to support this line of reasoning. However, maldistribution is not ordinarily considered to be sufficient cause for this degree of A-a O_2 difference at this point on the O_2 dissociation curve of hemoglobin (91 per cent O_2 saturation) when room air is being breathed. It is concluded, therefore, that a considerable impairment of "effective diffusion" must also exist in addition to the distribution defect.

Another serial study of a somewhat different

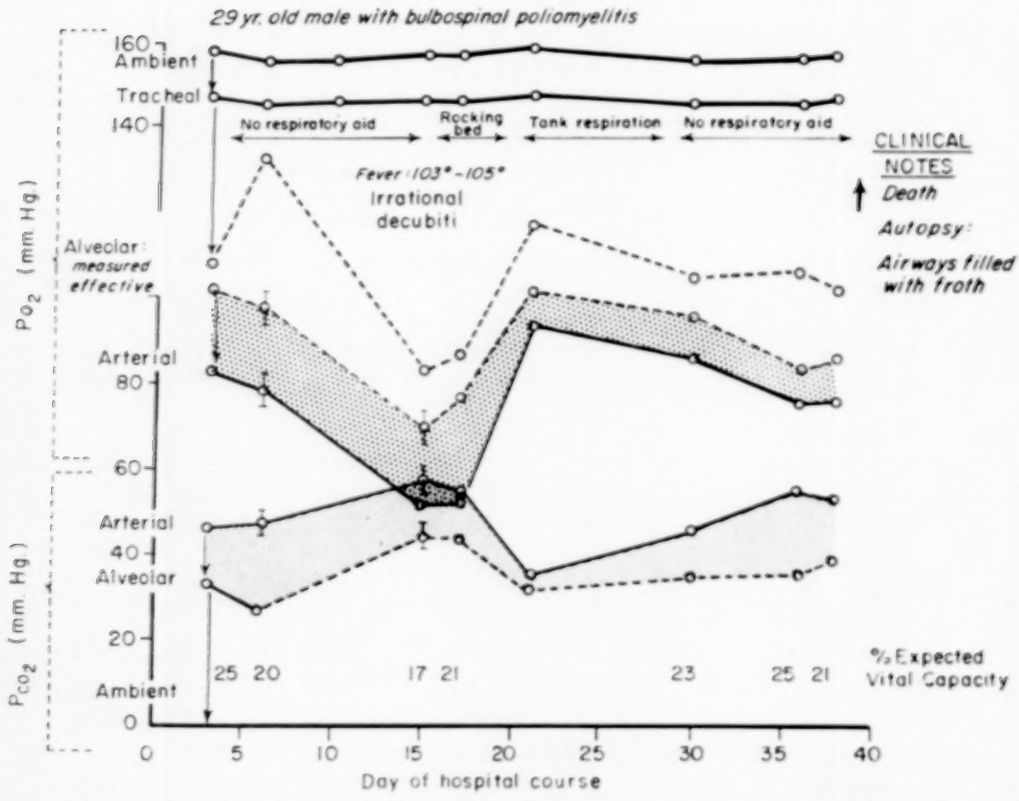

FIG. 10. Serial study of respiratory gas tension relationships in the course of fatal bulbospinal poliomyelitis.

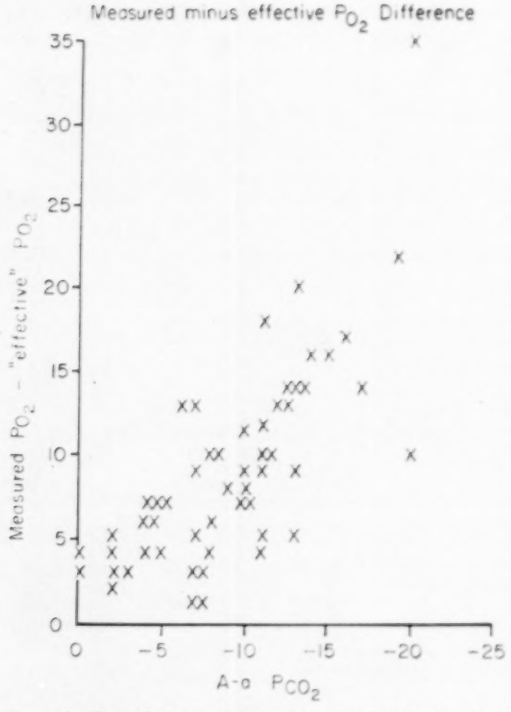

FIG. 11. Correlation of the measured-effective P_{O_2} difference with A-a P_{CO_2} difference.

type of patient with bulbospinal poliomyelitis is presented in Figure 10. This man was in the unfortunate position of retaining borderline respiratory capacity, with vital capacities in the marginal range of 17 to 25 per cent. Consequently, only after hypoventilation had developed on the sixteenth day of hospitalization did he receive mechanical aid to his respiration. The alveolar and arterial gas tensions indicate that the rocking bed was not sufficient to give adequate ventilation (sixteenth to twentieth days), whereas the tank respirator on the twenty-first day gave adequate ventilation. Its use was discontinued on the twenty-eighth day because the patient appeared to be doing well. The hypercapnia and hypoxemia gradually returned by the thirty-sixth day. The A-a CO_2 differences encountered here were as great as any in the entire study, and yet were not accompanied by markedly increased A-a O_2 differences. This is taken to indicate that non-uniform distribution *per se* probably causes little increase in the A-a O_2 difference [*21*]. However, non-uniform distribution would theoretically cause an increase in the difference between measured

and calculated "effective" alveolar O_2 proportionate to the A-a CO_2 difference. This seems to be the case as these differences are followed serially in Figure 10. The correlation can be seen more clearly in Figure 11. Inaccuracies in methodology at the present time probably prevent better correlation.

On the seventeenth day the greatest O_2 gradient (24 mm. Hg) for the patient in Figure 10 occurred, when the alveolar O_2 tension was 70 mm. Hg, and the arterial CO_2 tension was 54 mm. Hg. Calculated end pulmonary capillary O_2 saturation would be 91 per cent; therefore, a moderate diffusion barrier may have existed at that time. This may have been due to an edematous alveolar-capillary membrane or a reduction of the area of blood-gas interphase during hypoventilation resulting in maldistribution of blood and gas in the lungs. The arterial O_2 saturation was on the steeper portion of the O_2 dissociation curve for hemoglobin, and therefore at a point where venous admixture or maldistribution *per se* could make little difference. It is noteworthy that not only ventilation but also diffusion and distribution were restored to normal by use of the tank respirator. After withdrawal of respiratory equipment nonuniform distribution again became apparent with a growing A-a CO_2 difference. It is curious that as ventilatory insufficiency returned, as evidenced by rising CO_2 tensions, diffusion apparently remained nearly normal with A-a O_2 differences of 8 to 10 mm. Hg at 90 per cent arterial O_2 saturation.

The two patients with bulbospinal poliomyelitis presented in Figures 6 and 10, and other serial studies not reported here, demonstrate the common pitfalls in the management of acute poliomyelitis patients with respiratory paralysis. First, in Figure 7, the use of ventilatory measurements, such as tidal volume, minute ventilation or alveolar CO_2, to determine the adequacy of gas exchange proves to be misleading. The patient represented in Figure 6 had more than adequate ventilation in terms of minute volume at all times; his alveolar ventilation even exceeded normal. Therefore, if his respiratory assistance had been decided on the basis of measurements of tidal volume, minute volume, alveolar CO_2 or even arterial CO_2 and pH, there would have been no concern for the serious degree of hypoxemia which developed. Cyanosis in a situation like this may not be apparent because the respiratory alkalosis will shift the oxygen dissociation curve of hemoglobin to the left, resulting in near normal arterial O_2 saturation.

The second case, presented in Figure 10, demonstrated the unreliability of alveolar gas studies by themselves. Even when arterial P_{CO_2} was seriously elevated, alveolar CO_2 was still at the upper limits of normal. A true indication of the adequacy of CO_2 elimination was obtained from alveolar gas analysis at only one point, the twenty-first day, when the A-a CO_2 difference was only 4 mm. Hg. Use of respiratory equipment might have been delayed even longer if alveolar CO_2 had been used as a criterion. On the other hand, arterial blood analysis gave a truer picture at all times.

As methods for arterial blood gas analysis are improved and are more commonly available it will become practical as well as ideal to manage patients with respiratory paralysis or any type of pulmonary disease by serial arterial studies. Oxygen tension can now be measured in blood most accurately over a wide range by use of the Clark type of polarographic electrode [*22*]. Carbon dioxide tension can be measured most accurately by the use of a pH electrode [*23–25*] or a CO_2 electrode [*26*].

CONCLUSIONS

In the final analysis these serial studies of the alveolar-arterial gas tension relationships of acute poliomyelitis patients indicate that the incidence of specific defects in gas exchange were as follows: (1) ventilatory insufficiency (Pa_{CO_2} exceeding 42 mm. Hg) in 32 per cent of the cases; and (2) elevated ventilation-to-perfusion ratio (A-a P_{CO_2} exceeding 5 mm. Hg) in 50 per cent of the cases.

On the basis of this study of alveolar-arterial gas tension relationships it is concluded that the exchange of gases in the lungs may be impaired in any one or all conceivable ways in acute poliomyelitis with bulbar or bulbospinal involvement. Modern methods of gas tension analysis of alveolar gas and arterial blood permit identification of the specific disorder in critically ill respirator patients without requiring the patient's cooperation or the performance of respiratory maneuvers. In fact, some of the more severely ill patients were comatose in respirators while the function tests were being performed. Despite this, the adequacy of alveolar ventilation, the uniformity of inspired gas distribution, the diffusion gradient necessary

for the transfer of oxygen across the alveolar-capillary membranes, and the relative magnitude of venous admixture in the pulmonary circulation could be determined. Such laboratory data may prove extremely useful in determining when such a patient requires increased mechanical assistance to his respiration, when oxygen should be added to the patient's inspired air, when mechanical aids to cough should be employed in order to help raise secretions blocking airways or when attempts to re-expand atelectatic areas of the lungs have been successful. Such measurements should also help in the evaluation of prophylactic procedures such as occasional deep breaths, pulmonary physical therapy or surface-active aerosols to prevent airway obstruction and atelectasis from developing. This same approach has also been applied by the authors to other pulmonary diseases and has proven equally useful.

It is concluded that measuring only the minute ventilation or alveolar CO_2 in patients with seriously diseased lungs in order to evaluate the adequacy of gas exchange is not enough. Therapy based on such information, or calculations of ideal tidal volume from a nomogram based on age and weight [*14*], usually results in the use of inadequate respirator pressure settings in patients with acute poliomyelitis and many other types of pulmonary disease. The most reliable information for the treatment of acute pulmonary disease is obtained from arterial blood gas analyses.

SUMMARY

Alveolar gas and arterial blood samples were drawn simultaneously for ninety-six studies of O_2 and CO_2 tension in forty-nine patients with acute anterior poliomyelitis. Nine of the more severely afflicted patients were studied serially on four or more occasions.

With increasing respiratory paralysis and bulbar involvement, increasing impairment of gas exchange was found. (1) The most common defect in gas exchange was found to be non-uniform distribution of blood and gas in the lungs, resulting in alveolar-arterial (A-a) CO_2 tension differences exceeding 5 mm. Hg in 50 per cent of the ninety-six studies, and in 83 per cent of the fifty-three studies on patients with bulbospinal poliomyelitis requiring respiratory equipment. (2) Insufficient ventilation, resulting in an arterial P_{CO_2} exceeding 42 mm. Hg, was encountered in a third of the studies. (3) Venous admixture resulting in an A-a P_{O_2} difference greater than 20 mm. Hg when arterial oxygen saturation exceeded 93 per cent was found in a quarter of the studies. (4) Impaired diffusion resulting in an A-a P_{O_2} gradient of 18 to 24 mm. Hg with arterial O_2 saturation of 81 to 82 per cent was found in only two cases. However, only in these two cases did sufficiently low alveolar P_{O_2} develop to permit such a conclusion.

A new approach for quantitating non-uniform distribution of alveolar ventilation in relation to blood flow in the lungs by measurement of the A-a P_{CO_2} difference is described and discussed. It permits evaluation of increased ventilation in relation to blood flow in the lungs, as distinct from increased blood flow in relation to ventilation.

On the basis of these studies, it is concluded that respiratory equipment can be of value not only in correcting hypoventilation but also occasionally in improving gas distribution and diffusion.

The importance of serial determinations of arterial blood gas tensions over a period of days or weeks for effective management of critical and complicated cases of respiratory insufficiency is apparent when the results are compared with measurements of tidal volume, minute ventilation and alveolar gas tensions.

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Measurement of Gas Trapped in the Lungs During Acute Changes in Airway Resistance in Normal Subjects and in Patients with Chronic Pulmonary Disease*

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RECENTLY DuBois and Dautrebande [*1*], using the body plethysmograph to measure pulmonary airway resistance (R_A) and functional residual capacity (FRC), demonstrated that inhalation of aerosols of fine dust particles or carbachol caused a significant increase in pulmonary airway resistance in normal subjects. Inhalation of an aerosol of a sympathomimetic drug resulted in an immediate fall in R_A to below the control level. Furthermore, the re-administration of either carbachol or fine dust particles now failed to cause a rise in airway resistance. No significant change in the various partitions of the lung volume was recorded.

Bedell and associates [*2*] have demonstrated a significant difference in the FRC as determined by the plethysmographic method from that measured by the dilution method in patients with pneumothorax, pulmonary cysts or emphysema. They were of the opinion that this difference represented the volume of gas trapped in the chest. This is due to the fact that the plethysmographic method measures all the compressible gas in the chest whether or not it is in communication with the tracheobronchial tree, whereas the dilution methods measure only that volume of air which communicates with the airways during the time of the test. Normally, these two volumes are the same. Gas may be trapped in the lungs because of chronic organic disease, as in emphysema, or it may be temporarily trapped due to "bronchospasm," as in asthma. This study is an attempt to quantify trapped gas in the lungs due to the inhalation of aerosols of either carbachol or fine dust particles of aluminum dust.

MATERIAL AND METHODS

Twenty-eight subjects were studied and were divided into two groups, each consisting of seven normal subjects and seven patients with either asthma or other chronic pulmonary diseases. The effects of breathing carbachol were studied in group I, those of inhaling fine particles of aluminum in group II. The physical characteristics and diagnoses of each group are shown in Table I.

The two liquid aerosols, Aerolone Compound® (Lilly)‖ and carbachol (carbaminoylcholine, Merck),¶ used in this study were produced by a D-30 generator under 15 p.s.i. head pressure. As shown previously,

‖ Containing 0.25 per cent isoproterenol, 0.5 per cent cyclopentamine in a 50/50 propylene-glycol and water vehicle.

¶ Containing 1 per cent carbachol in a 50/50 propylene-glycol and water vehicle.

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this generator produces particles all below 0.5 μ in diameter with a mean count diameter of 0.04 μ [3]. The powdered aerosol used was McIntyre aluminum* (said to consist of particles more than 90 per cent below 1 μ in diameter) and was dispersed under low pressure (less than 1 p.s.i.) through three elutriator flasks as previously described [1]. The larger particles and, eventually, the natural aggregates were scrubbed out before reaching the mouthpiece at the top of the third flask.

Airway resistance was measured by the plethysmographic method of DuBois et al. [4]. The FRC was measured both by the plethysmographic method [5] and by a modification of the helium dilution method of Meneely and Kaltreider [6]. In twenty-seven normal subjects, including the fourteen reported here, the mean difference in consecutive determinations of FRC by both methods was 0.068 $\pm$ 0.26 L. To be significant, and therefore provide evidence for trapping, the FRC by the plethysmographic method should exceed the FRC by the helium method by 2 standard deviations, or 0.52 L. The expiratory reserve volume and vital capacity were obtained from a 9 L. spirometer record and corrected to BTPS (body temperature, ambient pressure, saturated with water). The maximal mid-expiratory flow rate was calculated from a record of a forced expiratory vital capacity from a Krogh spirometer at a recording speed of 2.5 cm. per second [7]. Nitrogen washout curves were recorded for seven minutes of O_2 breathing from a nitrogen meter† with the sampling needle placed just outside the mouth.

The procedure followed routinely and consecutively in all subjects of groups I and II was as follows: (1) two control determinations of R_A and functional residual capacity by the plethysmographic method (FRC_{Box}); (2) determination of the functional residual capacity by the helium dilution method (FRC_{He}), followed by a spirometer recording of the vital capacity and expiratory reserve volume; (3) determination of the maximal mid-expiratory flow rate from the best of two forced vital capacity records; and (4) repeat determination of R_A and $FRC_{(Box)}$.

This series of measurements took about twenty minutes to perform. The same procedure was repeated after the inhalation of constricting aerosols (either carbachol or aluminum dust) and again after breathing Aerolone, a dilating aerosol. In the majority of subjects constricting aerosols were re-administered and the procedure repeated again. The performance of tests requiring voluntary cooperation (vital capacity, expiratory reserve volume and forced expiratory vital capacity) was always accomplished by vigorous coaching.

In eight other subjects blood samples were obtained from an indwelling arterial needle after determination of $FRC_{(Box)}$ during control conditions and after inhalation of constricting aerosols. These blood samples were analyzed for oxygen and CO_2 contents by the manometric method of Van Slyke and Neil [8],

TABLE I
PHYSICAL CHARACTERISTICS AND DIAGNOSES OF THE NORMAL SUBJECTS AND PATIENTS IN GROUPS I AND II

Subject	Age (yr.) and Sex	Height (cm.)	Weight (kg.)	Diagnosis
Group I (Normal Subjects)				
J. F.	30, M	174	73	
A. L.	20, F	169	57	
D. S.	30, M	165	64	
J. H.	29, F	164	49	
K. B.	22, M	185	80	
S. R.	20, F	165	55	
H. C.	30, M	166	79	
Group I (Patients)				
K. C.	55, M	178	80	Emphysema
B. U.	61, M	173	64	Emphysema
T. N.	52, M	188	91	Cyst, upper lobe of left lung
J. G.	38, F	162	88	Asthma
M. F.	62, F	163	48	Emphysema
J. G.	18, M	180	73	Asthma
J. S.	59, M	178	88	Emphysema
Group II (Normal Subjects)				
F. L.	45, M	175	72	
K. D.	46, M	196	80	
P. P.	34, M	181	77	
K. B.	22, M	185	80	
J. F.	30, M	174	73	
H. C.	30, M	165	79	
A. S.	32, M	175	72	
Group II (Patients)				
E. W.	53, M	188	81	Emphysema
F. O.	57, M	175	68	Emphysema
W. L.	16, M	166	55	Asthma
M. R.	63, M	175	84	Emphysema
J. R.	62, M	165	55	Emphysema, inactive tuberculosis
J. V.	67, M	173	91	Emphysema
J. H.	36, M	178	85	Asthma

* Courtesy of McIntyre Research Foundation, Toronto, Canada.

† Model 300 AR, Custom Engineering Development Co., St. Louis, Missouri.

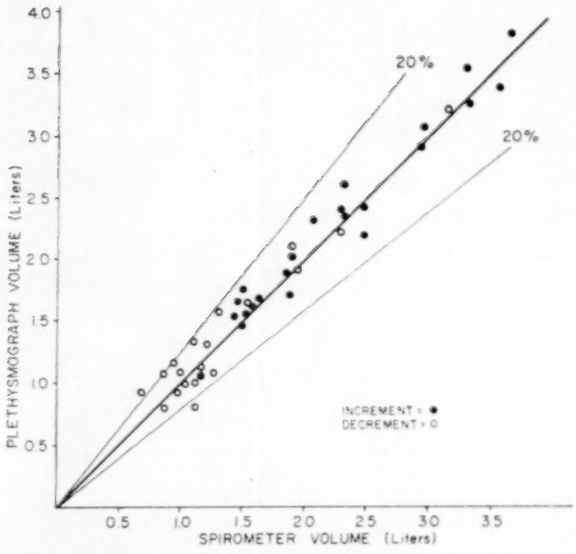

FIG. 1. Simultaneous determination of the volume of air added to or subtracted from a spirometer placed in the body plethysmograph and connected to a trained subject (H. C.). See text.

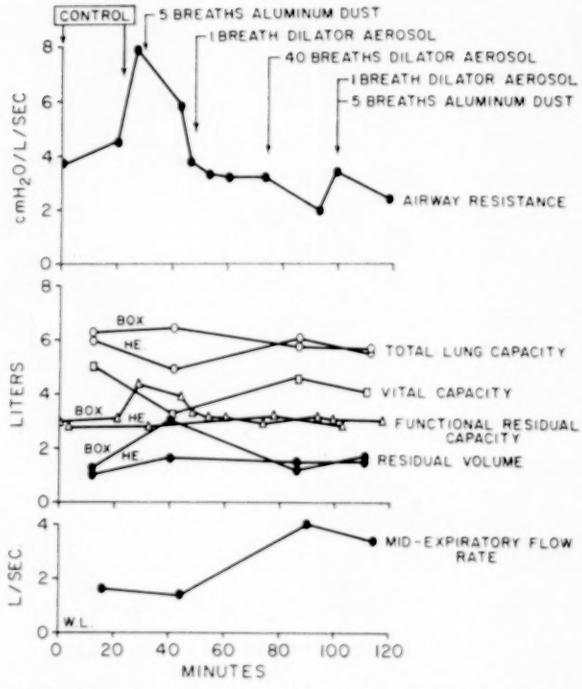

FIG. 2. Results of inhalation of aluminum dust in patient W. L. See text.

and for oxygen and CO_2 tension by the bubble method of Riley et al. [9].

In a few other subjects nitrogen washout curves were obtained in place of $FRC_{(He)}$.

To show that the plethysmographic method could reasonably measure volumes of air added to or subtracted from the lungs, the following procedure was followed. A recording spirometer was placed inside the plethysmograph and was connected to the distal side of the pneumotachygraph. After the FRC_{Box} was determined, the subject, on command, either inhaled from the spirometer or exhaled into it. The operator then closed the shutter in the circuit and the $FRC_{(Box)}$ was again determined. The difference between these two plethysmograph measurements was compared to the simultaneous volume added to or subtracted from the spirometer. Figure 1 shows this relationship. The mean difference was $0.049 \pm .160$ L.

RESULTS

Figure 2 shows the results of a typical experiment on a sixteen year old boy (W. L.) with a history of seasonal asthma. The control measurements revealed a normal partition of the lung volume and no trapped air but an elevated R_A and subnormal maximal mid-expiratory flow rate. Following five breaths of aluminum dust, R_A increased twofold and was rapidly accompanied by a difference of 1.5 L. between the FRC_{Box} and FRC_{He} and a decrease in the vital capacity of 1.75 L. One breath of the dilator aerosol resulted in an immediate drop in R_A to below the control level as well as a decrease in $FRC_{(Box)}$. After forty more breaths of dilator there was little change except that the maximal mid-expiratory flow rate rose to a normal level. Re-administration of the same number of breaths of aluminum dust failed to produce any further changes.

Tables II, III and IV, and Figure 3 summarize the results of breathing constricting and dilating aerosols for both groups studied. Only mean values and the ranges of minimal and maximal values are included. The results were not validly subject to statistical analysis because of the variability of the dose (number of breaths) of the three different aerosols. It was impossible to control this factor, especially in the patients, because of individual differences in response to the constricting aerosols. The direction of change to the constricting and dilating aerosols was consistent except where pointed out below.

Number of Breaths of Aerosols. There was a great deal of variability among the individual subjects. In general, normal subjects took considerably more breaths of the constricting aerosols than patients before a significant rise in both R_A and FRC_{Box} was produced. On the other hand, patients were given more dilator aerosol than normal subjects especially in group II. One or two breaths of the dilator aerosol was usually sufficient to reduce significantly R_A in

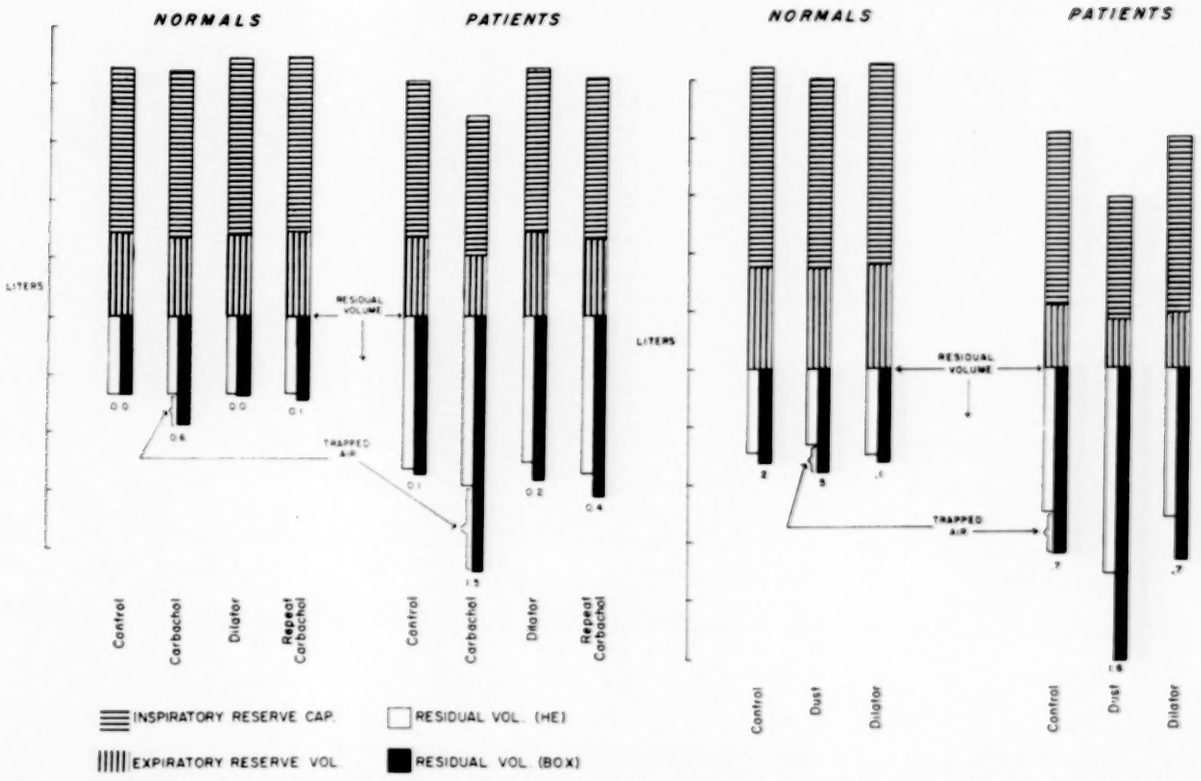

FIG. 3. *Left*, group I. *Right*, group II. In each column, the junction between the expiratory reserve volume and the residual volume is placed at the same level. The length of each column above this line represents the vital capacity. The difference in length of the two residual volumes represents the volume of trapped air.

both patients and normals, but it often took several more breaths to return the $FRC_{(Box)}$ towards the control value.

Airway Resistance (R_A). Both carbachol and aluminum dust caused a rise in R_A in every instance, the average increase being at least 100 per cent of the control value for both normals and patients. (Table IV.) There was one normal subject in group II who had an increase in R_A of only 0.5 cm. H_2O per L. per second. All of the remaining twenty-seven subjects showed a rise of R_A of at least 1.4 cm. H_2O per L. per second.

Trapped Air. Normal subjects: Both carbachol and aluminum dust caused an elevation in the volume difference between FRC_{Box} and FRC_{He} (trapped air). The average change in the amount of trapped air from control to constricting aerosol was just barely significant (0.52 L.) in the group breathing carbachol, but not in the group breathing aluminum dust. (Table IV.) However, three of the seven normal subjects in group I and four of the seven normal subjects in group II failed to show significant trapping.

Patients: Both constricting aerosols caused a marked degree of trapping in patients. The average absolute rise in trapped air was slightly more marked with those breathing aluminum dust. However, the change from the control value was less for this group because of an average control value for trapping of 0.7 L. as compared to 0.09 L. for the carbachol group. All but one patient had a significant rise in trapped air of greater than 0.52 L. when breathing constricting aerosols. The one exception was a patient breathing aluminum dust with an increase of 0.3 L. in FRC_{Box} while the FRC_{He} rose 0.8 L.

Lung Volume. The changes in the lung volume and its partitions are shown graphically in Figure 3. It is noteworthy that the vital capacity in the normal subjects was unaffected, while the patients showed a striking reduction of this parameter. This was especially marked in group II, in which all had a reduction of at least 0.5 L. and the average vital capacity with aluminum dust was 72 per cent of the control value. This reduction was more at the expense of the inspiratory reserve capacity than the expiratory reserve volume. Aerolone restored most of the parameters to the control value or greater.

TABLE II

EFFECTS OF BREATHING AEROSOLS OF CARBACHOL AND AEROLONE ON THE LUNG VOLUME (LITERS) AND BREATHING MECHANICS

(Mean Values and Ranges for Group 1)

	Normal Subjects				Patients			
	Control	Carbachol	Dilator	Repeat Carbachol	Control	Carbachol	Dilator	Repeat Carbachol
Number of breaths	...	31 (15–50)	10 (3–12)	22 (10–40)	...	8 (2–15)	13 (10–21)	9 (2–20)
Vital capacity	4.27 (3.04–5.54)	4.22 (3.20–5.21)	4.45 (3.30–5.75)	4.49 (3.30–5.75)	4.07 (2.81–6.26)	3.48 (2.15–5.62)	4.28 (3.01–6.63)	4.11 (2.80–6.58)
Inspiratory reserve volume	2.43 (1.75–2.80)	2.45 (1.91–2.85)	2.50 (1.91–3.06)	2.54 (1.75–2.96)	2.05 (1.21–2.99)	1.85 (.88–3.21)	2.18 (1.24–3.15)	2.11 (1.33–3.47)
Expiratory reserve volume	1.44 (0.88–2.21)	1.36 (0.93–1.96)	1.41 (0.98–2.12)	1.48 (0.87–2.04)	1.40 (0.63–2.52)	1.06 (0.48–1.77)	1.47 (0.97–2.46)	1.37 (0.75–2.35)
Residual volume (He)	1.33 (1.05–1.75)	1.32 (1.07–1.96)	1.33 (0.80–1.75)	1.34 (0.93–1.70)	2.66 (1.83–3.92)	2.94 (1.60–4.69)	2.57 (1.29–4.14)	2.73 (1.72–4.08)
Total lung capacity (Box)	5.66 (5.00–7.11)	6.15 (5.25–7.24)	5.84 (5.02–7.25)	5.93 (5.18–7.19)	6.81 (4.82–8.48)	7.90 (5.11–10.69)	7.12 (4.68–9.71)	7.25 (4.89–9.86)
Total lung capacity (He)	5.66 (4.64–6.99)	5.54 (4.92–6.61)	5.82 (4.60–7.26)	5.84 (4.79–7.20)	6.73 (4.84–9.95)	6.42 (4.25–9.10)	6.85 (4.30–9.90)	6.84 (4.52–9.84)
Functional residual capacity (Box)	2.77 (2.10–3.78)	3.25 (2.88–4.05)	2.78 (1.97–3.69)	2.92 (2.14–3.57)	4.14 (2.67–5.26)	5.49 (3.44–7.38)	4.32 (2.74–5.61)	4.52 (2.85–6.03)
Functional residual capacity (He)	2.77 (1.97–3.66)	2.68 (2.05–3.23)	2.81 (1.80–3.66)	2.83 (1.81–3.49)	4.05 (2.69–6.21)	4.00 (2.58–5.80)	4.05 (2.26–5.72)	4.10 (2.47–5.67)
"Trapped air"	0.00 (−.44–+.37)	0.57 (.09–1.37)	−0.03 (−.42–+.74)	0.09 (−.14–+.39)	0.09 (−1.47–+1.32)	1.49 (.86–2.11)	0.27 (−.19–+1.21)	0.42 (−.53–+1.77)
Airway resistance (cm. H_2O/L./sec.)	2.1 (1.6–2.7)	5.9 (3.1–11.1)	1.7 (1.0–2.2)	2.5 (2.1–3.1)	3.8 (1.3–5.9)	8.4 (3.2–11.6)	3.1 (1.5–4.8)	3.7 (1.6–6.4)
Maximal mid-expiratory flow rate (L./sec.)	4.1 (3.4–4.9)	3.4 (2.1–5.1)	4.5 (3.4–5.7)	3.8 (3.2–4.9)	1.2 (0.3–3.1)	1.1 (0.3–2.1)	1.7 (0.4–4.3)	1.6 (0.4–4.0)
Respiratory rate	13 (10–16)	14 (11–19)	12 (9–16)	12 (8–15)	14 (9–19)	16 (11–22)	15 (12–25)	14 (11–20)

TABLE III

EFFECTS OF BREATHING AEROSOLS OF ALUMINUM DUST AND AEROLONE ON THE LUNG VOLUME (LITERS) AND BREATHING MECHANICS

(Mean Values and Ranges for Group II)

	Normal Subjects			Patients		
	Control	Aluminum Dust	Dilator	Control	Aluminum Dust	Dilator
Number of breaths	...	12.4 (8–20)	13.9 (11–26)	...	5.4 (2–12)	29.4 (11–46)
Vital capacity	5.22 (4.20–6.15)	5.01 (4.02–6.32)	5.26 (4.30–6.37)	4.07 (3.07–5.00)	2.93 (2.14–3.84)	4.00 (2.69–4.86)
Inspiratory reserve volume	2.82 (2.28–3.24)	2.56 (2.20–2.97)	2.82 (2.45–3.24)	2.23 (1.54–2.97)	1.47 (1.09–2.11)	2.20 (0.98–3.68)
Expiratory reserve volume	1.77 (1.16–2.67)	1.78 (1.22–2.61)	1.80 (1.20–2.94)	1.13 (0.70–1.68)	.84 (0.38–1.19)	1.01 (0.38–1.68)
Residual volume (He)	1.45 (0.86–2.06)	1.38 (0.97–1.84)	1.44 (1.07–1.74)	2.46 (1.08–3.62)	3.43 (1.63–5.46)	2.60 (1.03–3.51)
Total lung capacity (Box)	6.87 (5.60–7.85)	6.79 (5.57–8.12)	6.84 (5.62–7.96)	7.21 (5.94–9.83)	7.99 (5.75–11.10)	7.29 (5.84–10.08)
Total lung capacity (He)	6.68 (5.36–8.11)	6.32 (5.12–7.84)	6.71 (5.50–7.84)	6.52 (5.10–7.78)	6.38 (4.55–8.41)	6.56 (5.48–7.68)
Functional residual capacity (Box)	3.41 (2.57–4.37)	3.64 (2.80–4.42)	3.38 (2.65–4.53)	4.28 (2.61–6.37)	5.85 (4.32–8.40)	4.31 (2.80–5.26)
Functional residual capacity (He)	3.22 (2.15–4.63)	3.16 (2.45–4.14)	3.25 (2.56–4.41)	3.58 (2.32–4.72)	4.24 (2.82–6.23)	3.58 (2.22–4.52)
"Trapped air"	0.19 (−.26–+.45)	0.48 (.03–1.19)	0.13 (−.13–+.44)	0.70 (−.03–+2.05)	1.61 (−.20–+3.91)	0.73 (−.13–+2.40)
Airway resistance (cm. H_2O/L./sec.)	1.7 (1.2–2.2)	4.8 (1.8–7.8)	1.4 (1.1–2.0)	3.3 (1.8–4.9)	7.0 (5.1–9.6)	2.6 (1.9–3.8)
Maximum mid-expiratory flow rate (L./sec.)	3.7 (3.1–5.1)	3.4 (2.6–3.9)	3.6 (2.7–4.6)	1.5 (0.4–4.4)	0.9 (0.4–1.8)	1.9 (0.9–4.0)
Respiratory rate	11.4 (8–13)	12.0 (10–16)	9.9 (5–14)	15.1 (10–19)	18.1 (14–26)	16.8 (15–22)

Maximal Mid-Expiratory Flow Rate. In general, there was a tendency for the flow rates to decline, and this was especially true for the patients in group II of which only one of seven failed to show some decrease in this test. However, some normal subjects and patients in both groups showed an increase in flow rate after inhaling constricting aerosols even though a concommitant increase in R_A developed in all subjects. This can only be interpreted to mean that the control forced vital capacity was submaximal even though optimal cooperation appeared to be elicited in all cases.

Nitrogen Washout Curves. Continuous breath-by-breath analysis of nitrogen concentration of expired air, as well as a Haldane-Priestley

TABLE IV

AVERAGE DIFFERENCE AND PER CENT CHANGE FROM CONTROL VALUES AND NUMBER OF SUBJECTS SHOWING DIFFERENCES FOLLOWING INHALATION OF CONSTRICTING AEROSOLS

	Airway Resistance			Trapped Air			Vital Capacity			Residual Volume (He)		
	Average Difference (cm. H_2O/L./sec.)	No. Increased	% Control	Average Difference (L.)	No. Increased >0.52 L.	% Control	Average Difference (L.)	No. Decreased >0.5 L.	% Control	Average Difference (L.)	No. Increased >0.5 L.	% Control
Group I (Carbachol)												
Normal subjects	+3.8	7	181	+0.57	4	00	−0.05	0	1	−0.01	1	1
Patients	+4.6	7	121	+1.40	7	1550	−0.59	4	14	+0.28	2	10
Group II (Aluminum Dust)												
Normal subjects	+3.1	7	182	+0.29	3	152	−0.21	1	4	−0.07	0	5
Patients	+3.7	7	112	+0.91	6	131	−1.14	7	28	+0.97	6	40

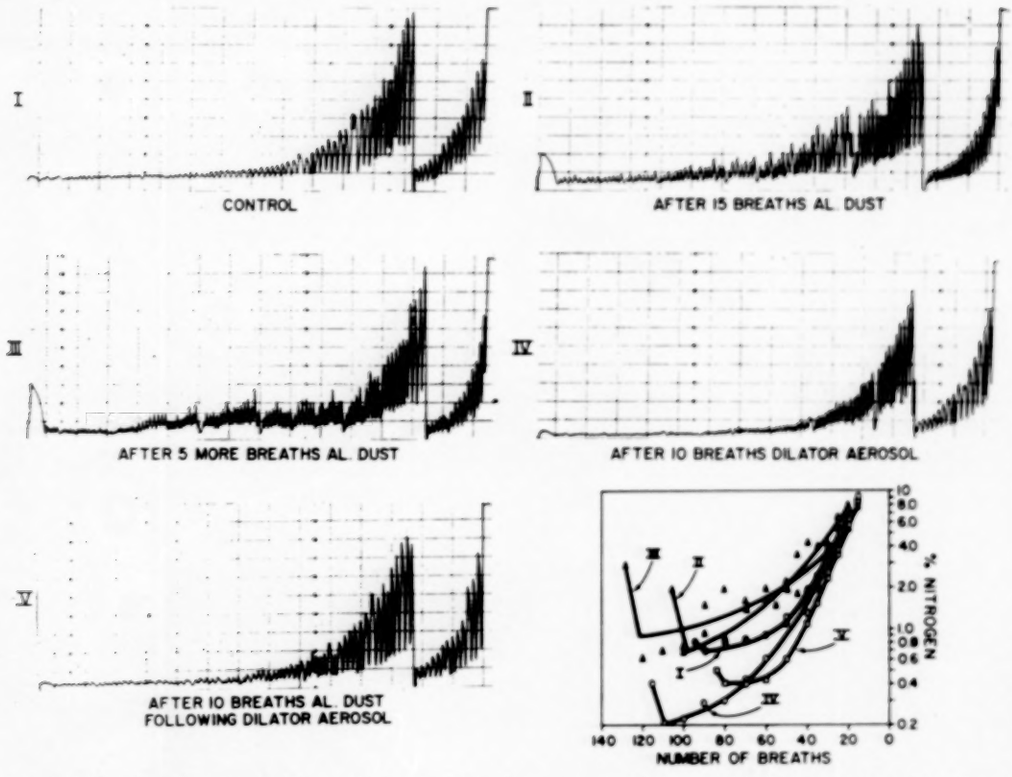

FIG. 4. The actual records of breath by breath nitrogen washout curves (I-V) in subject J. F. are shown. All records run from right to left; the early part of each record is in a scale of 0 to 100 per cent N_2, while the remainder is recorded on a 0 to 10 per cent N_2 scale. The last breath in each record is the N_2 concentration of a Haldane-Priestley sample. In the lower right corner each of the five curves have been replotted on semi-log scale. The index of intrapulmonary mixing was normal except when breathing aluminum dust..

sample after seven minutes of O_2 breathing, in a few other subjects before and after breathing constricting and dilating aerosols showed striking changes indicative of impaired distribution of gas in the lungs after bronchoconstriction. A representative set of such washout curves is shown in Figure 4 for normal subject J. F. The curve following the inhalation of a total of twenty breaths of aluminum dust was delayed and quite irregular compared to the control curve and the Haldane-Priestley N_2 concentration was 3 per cent (index of intrapulmonary mixing). This was associated with a rise in R_A from 1.2 to 6 cm. H_2O per L. per second and 0.5 L. elevation in FRC_{Box}. Following the inhalation of ten breaths of the dilating aerosol, the washout curve was improved over the control curve and R_A had fallen to below the control value of 1.3 cm. H_2O per L. per second. Repeat exposure to aluminum dust then failed to impair the washout curve.

Protective Effect of the Dilating Aerosol. Aerolone not only restored all values previously elevated by either carbachol or aluminum dust towards the control value or better, but also in most cases served to protect the lungs from the effects of further inhalation of the respective constricting aerosol. This effect is shown in Table II for the subjects breathing carbachol. Inhalation of aluminum dust was not repeated in two normal subjects and two patients in group II and, therefore, the averages for the remaining subjects in this group were not comparable to the other data. However, the protective effect of the dilating aerosol for these ten subjects was of the same magnitude as in group I.

There were two patients (K. C. and J. G.) in group I who failed to show any protective effect when carbachol was given after dilating aerosol. In each instance the rise in R_A and trapped air was almost as great as after the first administration of the drug. They were the only two patients in this group who received as much as a double dose on the second administration of carbachol.

One patient (M. R.) in Group II failed to show the protective action of dilating aerosol when aluminum dust was re-administered in the same dose as the first time. No subject in this group received more breaths of aluminum dust after dilating aerosol than he did on the first administration.

COMMENTS

In assessing the quite striking degree of gas "trapped" in the lungs during these acute experiments, it becomes pertinent to inquire into the validity of the measurement of the FRC by the plethysmographic method. We believe that these values are valid for the following reasons.

(1) In our series of consecutive determinations of the FRC in normal subjects by the helium dilution and the plethysmographic methods the mean difference was small (.068 ± 0.27 L.), which compares favorably with a similar series by DuBois [5] (0.0 ± 0.22 L.). A standard deviation of this amount is not surprising in consideration of the fact that in untrained subjects the resting breathing level may vary by 0.1 L. or more from breath to breath. Furthermore, the FRC_{He} represents the volume in the lungs at only the instant the subject is turned into the circuit, whereas FRC_{Box} is an average of at least four determinations at presumably the same resting level.

(2) Simultaneous measurement of air exhaled by a subject with a spirometer placed in the box or inhaled from the latter showed good agreement with the volume as measured by the plethysmographic method over a wide range. (Fig. 1.)

(3) The rapidity of the change in FRC_{Box} with both constricting and dilating aerosols and the relative stability of the values at other times (Fig. 2) was a consistent finding in every one of the twenty-one instances in which trapping was significant.

(4) Lastly, the close association between the occurrence of trapped air and impairment of distribution of inspired air as demonstrated by nitrogen washout curves was a constant finding in the subjects so studied. A few breaths of aluminum dust produced changes in the nitrogen washout curve of the normal subject in Figure 4 that are identical to the curve of patients with obstructive pulmonary emphysema. This was associated with the presumed "trapping" of 0.5 L. of air and an elevation of airway resistance. These changes were all reduced quickly by a few breaths of a potent bronchodilator. (Fig. 4.)

The profound changes in trapped air resulting from inhalation of either carbachol or aluminum dust are undoubtedly the result of constriction of the airways. This was manifested by the elevation in airway resistance and the marked effect on mixing and distribution of inspired air as well as a decrease in the vital capacity. It is likely that the smaller bronchioles and alveolar ducts were involved. Some of these passages were probably almost completely occluded as demonstrated by the inability of helium to penetrate into the areas distal to them during the time of testing. Gas was most likely trapped in the areas beyond the constricted airways. It was released slowly, as shown by the gradual fall of FRC_{Box} over fifteen to twenty minutes and also by the irregularity of the N_2 washout curve. Inhalation of the dilating aerosol caused a sudden fall in R_A and FRC_{Box} indicating that the constricted airways opened up rapidly.

Perfusion of such poorly ventilated areas result in an increase in the physiological right-to-left shunt and arterial oxygen desaturation. This possibility was studied in eight other patients and no correlation was found between the degree of gas trapping by constricting aerosols and the change in arterial blood oxygen tension or saturation. Although some patients did have significant lowering of these two parameters, there was no persistent trend in this direction. This may be due to a constriction of the pulmonary vessels supplying poorly ventilated areas and, therefore, no change in the ventilation: perfusion ratio.

The changes in normal subjects following the inhalation of constricting aerosols were unexpected. DuBois and Dautrebande [1], using the same agents, found no change in FRC_{Box} in five normal subjects, although a significant change in R_A was noted. However, the mean rise in R_A was not as great as we found. It is possible that their subjects were less sensitive to these agents, as was found in seven of our normal subjects.

The changes observed with constricting aerosols in the normal subjects were in the direction of the derangement usually found in patients with obstructive pulmonary emphysema, i.e., increased airway resistance, decreased M-EFR and timed vital capacity, as well as elevation of the index of intrapulmonary mixing and a slow nitrogen washout curve. This does not imply that the inhalation of dust or any constricting

agent is an etiological factor in the production of emphysema. But from these studies it would appear that dust inhalation causes temporary but marked physiologic changes in the lungs, including gas trapping even in normal subjects.

SUMMARY

Measurements of airway resistance and functional residual capacity (plethysmographic method), functional residual capacity (helium dilution method), various partitions of the lung volume, and the maximal mid-expiratory flow rate were performed in fourteen normal subjects and fourteen patients with chronic pulmonary disease before and after the inhalation of constricting aerosols (aluminum dust and carbachol) and a dilating aerosol. The normal subjects and patients were equally divided into two groups, one breathing carbachol and the other aluminum dust.

Increases in airway resistance were produced in every instance in both normal subjects and patients by both constricting aerosols. On the average, the rise was double the control value. This was accompanied by significant accumulation of trapped air (difference in volume of functional residual capacity by the two methods) in thirteen of the fourteen patients. Significant trapping occurred in half of the normal subjects.

The vital capacity was little affected in the normal persons but the average reduction from control values was 0.6 L. in patients breathing carbachol and 1.1 L. in those breathing aluminum dust.

Inhalation of a sympathomimetic aerosol restored all measurements towards the control value or better. A second inhalation of approximately the same number of breaths of the constricting aerosols demonstrated a protective effect of the sympathomimetic aerosol. This time significant elevations in any of the measurements occurred in only three instances. Two of the three exceptions were patients who received twice the number of breaths of carbachol on the second administration.

Continuous analysis of nitrogen in the expired air of several other normal subjects during oxygen breathing showed marked changes of intrapulmonary gas mixing associated with elevated airway resistance and probable trapping. The nitrogen washout curves returned to normal subsequent to inhalation of a sympathomimetic aerosol and remained normal after repeat inhalation of the constricting aerosol.

The amounts of intrapulmonary gas trapped, the reasons for the validity of the trapping measurements, and some of the probable mechanisms involved in its production are discussed.

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Blood Ammonia in Cerebral Dysfunction*

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INTEREST in the concentration of ammonia in the blood and its relation to neuropsychiatric disturbances has largely centered about liver disease. The identification of ammonia as the presumptive cause of the meat intoxication syndrome of Eck fistula dogs [*1*] has been followed by the repeated demonstration of abnormal blood ammonia levels in cirrhotic patients.

Recent investigations indicating the presence of abnormal ammonia concentrations in non-hepatic diseases [*2,3*], as well as the importance of non-hepatic sources of ammonia [*4*], warrant a further consideration of the relation of ammonia to cerebral function. It was the purpose of this investigation to study the venous blood ammonia level in patients with Laennec's cirrhosis and its various complications, including hepatic coma, and in patients with various non-hepatic disease entities with and without coma.

METHODS

The patients studied were admitted to the St. Louis City Hospital and John Cochran Veterans' Administration Hospital during a twelve-month period. A blood sample was obtained on admission from all disoriented or comatose patients, and from all patients thought to have Laennec's cirrhosis whether disoriented or not. After diagnostic study and clinical observation the patients were classified into four groups: (1) cirrhosis without coma, (2) cirrhosis with hepatic coma, (3) cirrhosis with coma or confusion not due to hepatic insufficiency, and (4) coma of varied etiology in patients with no evidence of liver disease. The classification was made without knowledge of the blood ammonia level.

In most patients the diagnosis as cirrhosis was confirmed by microscopic study of liver tissue obtained at liver biopsy or at autopsy. All were chronic alcoholics without evidence of liver disease other than Laennec's cirrhosis. Jaundice and/or ascites and/or hepatomegaly was present in each. Liver function studies in the cirrhotic and alcoholic patients included the cephalin cholesterol flocculation test, thymol turbidity test, total and fractional serum proteins, serum alkaline phosphatase, serum bilirubin, prothrombin time and in some cases the glutamic oxaloacetic transaminase level.

Some of the patients designated in this study as alcoholic without cirrhosis also had laboratory evidence of liver dysfunction. In the absence of microscopic liver examination or such physical evidence of chronic liver disease as jaundice, ascites, hepatomegaly or vascular spiders, an alcoholic was arbitrarily considered to be non-cirrhotic if the cephalin cholesterol flocculation was not greater than 2 plus at twenty-four hours, the bromsulphalein retention was not greater than 20 per cent at thirty minutes after a 5 mg. per kg. dose, and the serum albumin was greater than 3.5 gm. per cent. The diagnoses in the other disease entities conformed to the usual clinical criteria and were made after adequate diagnostic examinations and careful observation.

Determinations of blood ammonia were made according to the Conway microdiffusion method [*5*]. The time of diffusion was ten minutes. Blood samples were drawn from the brachial vein into a syringe and immediately transferred to tubes containing sodium heparin as an anticoagulant. Determinations were made in triplicate in each sample. All samples were run within forty-five minutes after withdrawal. The effect of time on the diffusible ammonia content of both aerobically and anaerobically drawn specimens is shown in Figure 1, which indicates that the error introduced by variation in time elapsing from venipuncture to analysis in our experiments was not more than 5 μg. per 100 cc. This relationship of ammonia content to time is in accord with Conway's finding of an increase in ammonia of shed blood occurring at the rate of 0.43 μg. per 100 cc. per minute after the first ten minutes following withdrawal.

RESULTS

Ammonia determinations performed by the method described in fifty-two healthy housestaff

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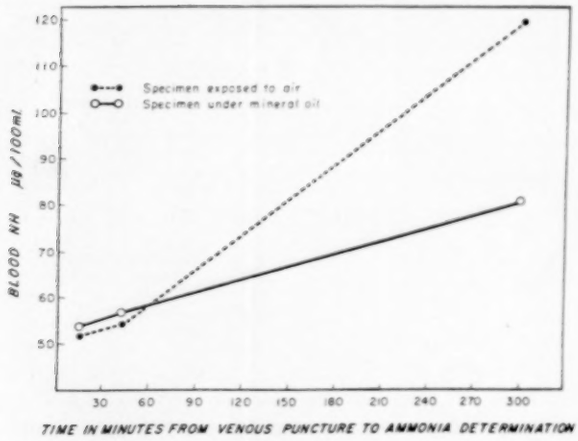

FIG. 1. The effect of time and exposure to air on ammonia concentration.

and hospital personnel gave a mean value of 55 ± 12 µg. per 100 cc. of blood with a range of 25 to 79 µg. per 100 cc. Serial determinations in these subjects revealed minimal daily variation.

Table I gives a summary of the data obtained in hospitalized patients who had neither cirrhosis nor mental disturbances including coma. A marked elevation to a level of 130 µg. of ammonia per 100 cc. of blood occurred in a patient with thrombosis of the portal vein and esophageal varices. His liver appeared normal at laparotomy, and a biopsy specimen of the liver showed no evidence of cirrhosis. This patient seems to demonstrate clearly the effect of a portasystemic shunt on the level of ammonia in the systemic circulation. A second patient with significant ammonia elevation in this group was a chronic alcoholic who was hospitalized with acute gastrointestinal bleeding from a duodenal ulcer. Although the patient did not fit the criteria of cirrhosis as established in this study, there was bromsulphalein retention of 15 per cent at thirty minutes and a serum albumin of 3.8 gm. per 100 cc. This dysfunction, together with the increased absorption of ammonia occurring after gastrointestinal hemorrhage, may explain the increase in blood ammonia level. The patients with choledocholithiasis were jaundiced and had abnormal reactions to cephalin cholesterol flocculation tests at the time the normal blood ammonia values were obtained.

Table II shows the ammonia levels during coma caused by entities other than hepatic failure. One patient in a semi-stuporous, disoriented state, suffering from acute alcoholic intoxication and massive upper gastrointestinal hemorrhage, had an ammonia level of 106 µg. per 100 ml. While a significant elevation over the normal, this value was lower than any encountered in patients with hepatic coma. The ammonia values in the uremic patients were all in the low normal range.

Ammonia levels in cirrhotic patients classified according to clinical status and complications appear in Table III. A mean value of 182 µg. of ammonia per 100 cc. of blood, with range of 127 to 350 µg., was found in patients in hepatic coma. Of the seven patients without ascites or jaundice, only one had an ammonia level higher than that of the normal subjects. One-third of the patients with ascites or jaundice but clear sensorium had

TABLE I

BLOOD AMMONIA IN HOSPITALIZED PATIENTS WITHOUT CIRRHOSIS AND WITHOUT COMA

Disease	No. Patients Studied	Blood Ammonia	
		Mean (µg./100 ml.)	Range (µg./100 ml.)
Pulmonary fibrosis and emphysema	7	56	34–90
Choledocholithiasis	3	58	46–73
Congestive failure secondary to hypertension and arteriosclerosis	4	55	43–82
Uremia secondary to hypertension and nephrosclerosis	7	55	38–72
Alcoholism	13	59	33–75
Peptic ulcer	2	78	62–95
Peptic ulcer with hemorrhage	7	71	35–119
Portal vein thrombosis	1	130	130
Hepatic metastases secondary to bronchiogenic carcinoma	2	89	82–96

TABLE II

BLOOD AMMONIA IN COMATOSE PATIENTS WITHOUT CIRRHOSIS

Disease	No. Patients Studied	Blood Ammonia	
		Mean (μg./100 ml.)	Range (μg./100 ml.)
Cerebral vascular accidents	11	61	37–85
Cerebral trauma	5	53	26–86
Alcoholic psychoses	8	64	38–106
Uremia secondary to hypertension	3	36	19–51
Drug intoxications	7	57	34–79
Febrile delirium with pneumonia	2	50	30–71
Congestive failure secondary to arteriosclerosis	2	64	52–70
Carcinoma of the lung	1	59	59

levels as great as those occurring in patients with hepatic coma. Marked elevations of the systemic venous ammonia in the absence of coma also occurred in cirrhotic patients with gastrointestinal hemorrhage. Hemorrhage secondary to esophageal varices was not accompanied by greater ammonia elevation than hemorrhage from peptic ulcer. In a patient with normal cerebral function, whose liver biopsy was diagnostic of Laennec's cirrhosis, an ammonia level of 130 μg. per 100 cc. occurred during an acute episode of congestive heart failure due to rheumatic valvular disease. Three cirrhotic patients, disoriented and tremulous on admission and whose subsequent course led to a diagnosis of delirium tremens, had ammonia levels of 53, 59 and 89 μg. per 100 cc.

Table IV shows the clinical course, blood ammonia and serum electrolytes in the three patients with respiratory acidosis and coma resulting from it. All had significant blood ammonia elevations. Two of the three were well within the range of ammonia concentration found in hepatic coma. There was no clinical or laboratory evidence of cirrhosis. One of the three, (V. M.) had been taking 500 mg. of chlorothiazide daily for a seven-day period at the onset of coma. Treatment in these patients consisted of the administration of bronchodilators, oxygen, antibiotics and cortisone. In the two patients who recovered, ammonia levels which were elevated during coma returned to normal as the other electrolytes also improved. In the seven patients with chronic lung disease whose ammonia levels (listed in Table I) were normal, mental aberrations were absent. Some of these

TABLE III

BLOOD AMMONIA IN LAENNEC'S CIRRHOSIS

Disease	No. Patients Studied	Blood Ammonia	
		Mean (μg./100 ml.)	Range (μg./100 ml.)
Cirrhosis without ascites or jaundice	7	76	59–104
Cirrhosis with ascites or jaundice	15	109	55–179
Cirrhosis with gastrointestinal hemorrhage	7	131	92–200
Hepatic coma	18	182	127–350
Cirrhosis with delirium tremens	3	67	53–89
Cirrhosis with congestive failure secondary to rheumatic valvular deformity	1	130	130
Cirrhosis with prior portocaval shunt	2	176	127–225

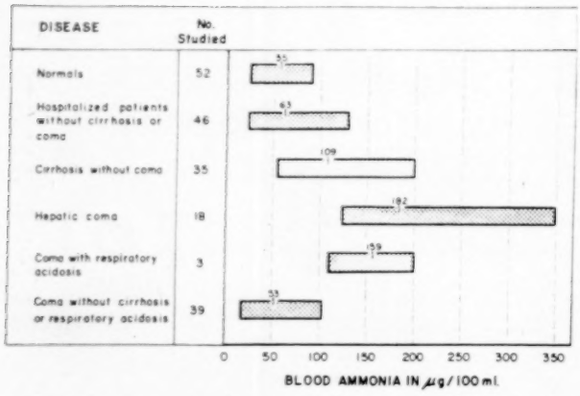

FIG. 2. The range and mean of blood ammonia levels. (Figures above bars indicate mean values.)

patients had laboratory evidence of equally marked carbon dioxide retention. The blood ammonia values in all patients studied, as well as the normal subjects, are summarized in Figure 2. Coma secondary to hepatic failure and coma secondary to respiratory acidosis are clearly separated from coma due to other cause in terms of the blood ammonia concentration. The considerable overlap in ammonia level between mentally clear cirrhotic patients and cirrhotic patients in coma also is evident.

COMMENTS

Certain difficulties are encountered in the determination and evaluation of blood ammonia levels. Lack of standardization of the diffusion method may have been the cause of a lack of consistency in normal and abnormal values in different laboratories. Furthermore, the origin of the ammonia liberated by alkalinization of the blood specimen is not firmly established. As stated by Conway [*5*], the release of carbon dioxide from venous blood in contact with air is accompanied by an initial rapid liberation of ammonia. Then a slower, continuous production of ammonia follows, the precursors of which are thought to be adenyl pyrophosphate or adenylic acid and glutamine. The relative importance of these compounds has not been established and other precursors have not been definitely excluded.

Many studies have attempted to correlate ammonia levels with the degree of cerebral dysfunction in hepatic failure. From these studies it seems fairly well established that while neurologic and psychic abnormalities occurring in cirrhotic patients are frequently accompanied by elevated blood ammonia levels [*6,7*], the correlation between height of ammonia level and degree of cerebral abnormality is by no means absolute. Such correlation is apparently greater with arterial ammonia concentrations than with venous blood ammonia concentrations [*8*]. The ammonia appearing in abnormal concentration arises principally from the gastrointestinal tract [*9*]. The ingestion of protein [*10*], ammonium chloride [*11*] and blood [*12*] have caused venous blood ammonia elevations in certain cirrhotic patients. The ammonia elevations following infusions of protein hydrolysate [*13*], use of Diamox® [*14*] and cation exchange [*15*] resins indicate that factors other than simple increase in gastrointestinal absorption of ammonia may be important. Such elevations of systemic blood ammonia are often accompanied in cirrhotic patients by mental confusion or coma, and in some instances improvement in cerebral status and decrease in blood ammonia concentration follow the infusion of L-arginine [*16*] or glutamic acid [*17*], and particularly after the use of antibiotics [*18–20*], which depress gastrointestinal bacteria and presumably increase the intestinal production and absorption of ammonia.

In the cirrhotic patients herein described

TABLE IV

BLOOD AMMONIA IN COMATOSE PATIENTS WITH RESPIRATORY ACIDOSIS

Patient	Date	Mental State	Diagnosis	Ammonia (μg./100 ml.)	Sodium (mEq./L.)	Chloride (mEq./L.)	CO_2 Combining Power (mEq./L.)	Potassium (mEq./L.)	Blood Urea Nitrogen (mg./100 ml.)
L. R.	5/15	Coma	Emphysema	162	139	92	38.4	5.5	
	6/2	Clear	Emphysema	51	138	91	31.3	4.7	17
V. M.*	3/1	Coma	Emphysema	200	136	84	40	3.9	12
	3/3	Clear	Fibrosis	98			34.2		
C. B.†	8/10	Coma	Pulmonary fibrosis	114	136	88	46.0	3.9	57

* Receiving Diuril at onset of coma.
† Died without regaining consciousness.

there was a good correlation between venous blood ammonia concentration and the severity of the liver disease as judged clinically. The highest ammonia concentrations were found in patients with hepatic coma. However, mentally clear cirrhotic patients who exhibited jaundice, ascites or gastrointestinal hemorrhage often had venous ammonia levels comparable to those found in patients with hepatic coma. This lack of correlation between systemic blood ammonia levels and central nervous system symptomatology indicates that if ammonia is indeed directly implicated in the cerebral dysfunction, other factors modify the concentration of ammonia at which this cerebral effect becomes manifest. The work of Warren and Nathan [*21*], for example, indicates that the blood pH is important in determining the rate and direction of diffusion of the unionized ammonia. Hydrogen ion and possibly other electrolytes may thus be important in modifying the effect of a given blood ammonia concentration on cerebral function.

In the cirrhotic patient a decreased rate of urea synthesis from ammonia might be expected [*22*]. The relative importance of impaired urea synthesis and portasystemic shunts in the production of abnormal blood ammonia levels in cirrhotic patients is uncertain. In our patient with portal vein thrombosis, examination of the liver at the time of surgery, and liver biopsy specimen also, revealed no cirrhosis and yet the blood ammonia was 130 μg. per 100 cc. In this patient the predominant factor in blood ammonia elevation seemed to have been the portasystemic shunts. Two cirrhotic patients who had previously had portacaval shunts because of bleeding from varices also showed marked ammonia elevations at a time when liver function seemed otherwise adequate.

Elevated blood ammonia has been reported in shock [*23*], congestive heart failure [*24*], with pulmonary emphysema [*27*] and with respiratory acidosis [*3*]. Our patients with congestive heart failure but without cirrhosis did not show ammonia elevation, but the single cirrhotic patient with heart failure secondary to rheumatic valvular disease appeared to have a greater ammonia concentration than would have been expected from the status of his liver disease alone.

The striking venous blood ammonia elevations, comparable to those of hepatic coma, found in the three comatose patients suffering from respiratory acidosis secondary to well established lung disease is of great interest. In the two in whom cerebral symptoms disappeared during therapy, the clinical improvement was accompanied by a return to normal of the previously increased blood ammonia. These three patients had no clinical or laboratory evidence of cirrhosis, nor was there evidence of portasystemic shunts. Confirmation of the clinical impression was obtained at autopsy in the third patient in whom the liver showed only congestion. While all three were in some degree of right heart failure with subsequent hepatic congestion, it seems unlikely that liver dysfunction played an appreciable part in the production of the increased blood ammonia. The cause and mechanism of systemic blood ammonia elevation during respiratory acidosis and its significance in the pathogenesis of the coma or respiratory acidosis are presently under investigation.

CONCLUSION

A study of venous blood ammonia concentrations in cirrhotic patients, comatose and noncomatose, and in patients with coma but without hepatic disease, indicates that in comatose patients significant elevation of the blood ammonia levels occurs only in hepatic failure and respiratory acidosis secondary to pulmonary disease. In cirrhotic patients, however, abnormal blood ammonia elevation may occur without evidence of cerebral dysfunction and it seems that portasystemic shunting may be an important, perhaps the most important cause of this elevation.

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Idiopathic Eosinophilic Infiltration of the Gastrointestinal Tract, Diffuse and Circumscribed*

A Proposed Classification and Review of the Literature, with Two Additional Cases

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RECENTLY we have encountered two patients with diffuse massive eosinophilic infiltration of the stomach with thickening and obstruction of the pylorus. One patient, in addition, had involvement extending from the duodenum to the mid-jejunum. Both had eosinophilia in the peripheral blood.

Since this rare but striking disorder has been described only in widely scattered reports throughout the world literature in the past decade, it seemed appropriate to attempt to classify and summarize our present knowledge of the subject.

CLASSIFICATION

Rational classification of disease is best developed out of an understanding of etiology. Many speculations have arisen regarding the mechanism precipitating eosinophilic gastroenteritis; however, no conclusive etiologic agent has been demonstrated to date. Emphasis has been given to hematogenous [*11,14*], and local gastrointestinal allergens [*5,14*], and foreign body reactions have been suspected in some cases [*2,6,54*]. Efforts to incriminate parasitic agents have been unavailing [*2,4,5,7,8,11*], and in the few instances in which fungi or bacteria have been noted in the microscopic sections this association is not convincing [*6,13*].

Lacking a precise knowledge of causal factors we should like to propose what is at best a provisional classification based on the pathologic and clinical picture derived from a study of the literature as well as our own patients. (Table I.)

Class I. Diffuse Eosinophilic Gastroenteritis

Group A. Polyenteric Type (eleven patients including (L. A.) reported on herein). Pathology (Table II): These patients were characterized by an extensive thickening and induration of the antrum extending throughout the small bowel to involve the jejunum or ileum. Some areas were firm and cartilaginous (particularly the pylorus), whereas others appeared vascular and edematous. In five patients, including our own, the surgeon was impressed by the gross similarity to regional enteritis. On occasion the omentum and mesentery were inflamed, boggy or fibrotic; hyperplastic nodes and ascites were often present. The serosa appeared reddened, with yellow or greyish patches. The pylorus was

TABLE I
CLASSIFICATION OF IDIOPATHIC EOSINOPHILIC INFILTRATION OF THE GASTROINTESTINAL TRACT

Class I. Diffuse Eosinophilic Gastroenteritis
Group A. Polyenteric (Barrie et al. [*2*])
Group B. Monoenteric (Ruzic et al. 1952 [*11*])
Group C. Regional (Kayser 1937 [*14*])
Class II. Circumscribed Eosinophilic-Infiltrated Granuloma
Group A. Regional (Kofler 1954 [*20*])
Group B. Polypoid (Vanek 1949 [*40*])

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TABLE II

DIFFUSE EOSINOPHILIC GASTROENTERITIS (CLASS 1)

Case No.	Age (yr.) and Sex	Location				History and Findings			Laboratory		Added Gross Findings				Microscopic Pathology				Course		Treatment			Authors
		Stomach	Duodenum	Jejunum	Ileum	Gastrointestinal Complaints (yr.)	Pyloric Obstruction	Allergy or Asthma	% Eosinophils in Blood	White Blood Cells per 1,000 cu. mm.	Ascites	Mesentery	Omentum	"Regional Enteritis"	Predominant Layer Involved	Perivascular Eosinophilia	Perineural Eosinophilia	Lymphadenopathy	Recurrences	Persistent Eosinophilia	Surgery	Biopsy	Corticosteroids	
Group A. Polyenteric																								
1	47,F	+	+	+	+	25	Yes	None	24	7	...	+	...	+	Sm, M, S	+	...	+	Yes	...	Yes	...	...	Swarts et al. Case 1, 1955 [1]
2	27,F	+	+	+	...	4	Yes	None	31	17	...	...	...	...	Sm, M	...	...	+	...	Yes	Yes*	...	...	Barrie et al. 1948 [2]
3	57, F	+	+	+	...	3	Yes	None	(12)	(8)	+	...	+	+	Sm, M	...	...	...	...	...	...	Yes	...	Maloney 1949 [3]
4	40,M	+	+	+	...	11	Yes	Yes	45	16	...	...	...	...	M	...	...	...	Yes	...	Yes*	...	...	Spencer et al. 1950 [4]
5	38,F	+	+	+	...	8	None	Yes	...	...	...	...	...	+	Sm, M, S	...	...	+	...	...	Yes*	...	ACTH	Orr et al. Case 1, 1954 [5]
6	35,M	+	+	+	...	8	Yes	None	(11)	...	...	...	+	...	Sm, M	...	+	...	...	...	Yes	...	...	Lynch et al. 1956 [6]
7	40,F	+	+	+	...	10	Yes	None	59	17	...	...	...	...	M	+	...	...	...	Yes	Yes*	...	...	Gentin 1956 [7]
8	23,M	+		+	...	11	Yes	Yes	21	13	...	+	...	+	M	...	...	+	Yes	Yes	Yes	...	ACTH	Ferrier et al. 1957 [8]
9	53,F	+	+	+	...	None	Yes	Yes	54	12	+	...	...	...	Sm, M	...	...	...	...	Yes	Yes	...	ACTH	Johnson et al. 1958 [9]
10	45,F	+	+	+	...	5	Yes	Yes	52	21	+	...	...	+	Sm, M, S	...	...	...	Yes	Yes	Yes	...	Cortisone	Our Case 1, 1960
11	34,M	+	+	...	...	None	Yes	Yes	54	24	...	...	...	...	Sm, M	...	...	...	...	Yes	Yes	...	...	Judd et al. 1955 [10]
Group B. Monoenteric																								
12	53,M	+	...	...	...	None	Yes	Yes	53	11	...	...	...	...	Sm, M, S	+	...	...	...	Yes	...	Yes	...	Ruzic et al. 1952 [11]
13	28,F	+	...	...	...	1	Yes	No	59	13	...	...	...	...	Sm, M	+	...	...	...	...	Yes	...	...	McCune et al. Case 1, 1955 [12]
Group C. Regional																								
14	55,M	+	+	+	+	Years	Yes	No	0'20'	17	...	...	...	...	Sm, M, S	...	+	...	...	...	Yes*	...	...	Herrera et al. 1948 [13]
15	53,M	+	...	...	...	Years	No	Yes	'29'	...	...	...	...	...	Sm, M, S	+	...	...	...	...	Yes	...	...	Kayser 1937 [14]
16	64,M	+	...	...	...	1	No	No	1	9	...	...	...	...	Sm, M	+ + +	...	...	...	...	Yes	...	...	Shneider et al. 1948 [15]
17	39,M	+	...	...	...	2	No	No	10	10	...	...	...	...	Sm, M, S	+ + +	...	+	...	...	Yes	...	...	Doniach et al. 1951 [16]
18	58,F	+	...	...	...	15	Yes	Yes	'10'	7	...	...	+	+	Sm, M	...	...	...	...	...	Yes	...	...	Barnett et al. 1952 [17]
19	42,F	+	...	...	...	7	Yes	Yes	'I'	...	...	...	...	...	Sm, M	+ +	...	...	Yes	Yes	Yes	...	...	Orr et al. Case 2, 1954 [5]
20	54,M	+	...	...	...	7	Yes	No	'I'	...	...	...	...	...	Sm, M	+	...	...	...	Yes	Yes	...	...	McCune et al.
21	30,M	+	...	...	...	...	Yes	No	2	10	...	...	...	...	Sm,	...	...	...	...	...	Yes	...	...	Cases 2 and 3, 1955 [12]
22	33,M	+	...	...	...	None	Yes	No	47	12	...	...	...	...	Sm, M, S	+	...	...	...	...	Yes	...	...	Swarts and Young, Case 2, 1955 [1]
23	36,M	+	...	...	...	15	None	No	0'5'	5	...	...	...	...	Sm	...	...	...	...	...	Yes*	...	...	Van Der Linden 1957 [18]
24	47,M	+	...	...	...	None	None	No	'0'	...	...	...	...	...	Sm, M	...	...	...	...	...	Yes	...	...	Houghton 1959 [19]
25	21,M	+	...	...	...	8	Yes	Yes	9'16'	10	...	...	...	...	Sm, M, S	+	+	+	Yes	Yes	Yes	...	...	Our Case 2, 1960

NOTE: ( ) indicate blood studies on previous admission; ' ' indicates postoperative blood studies; ↑ indicates increased. Sm indicates submucosa; M indicates muscularis; S indicates serosa.
* Indicates difficult anastomosis due to edema.

usually narrowed and hypertrophied, measuring 10 to 25 mm. in width.

Microscopically, there was a diffuse chronic inflammatory infiltrate extending from the submucosa up to and at times including the serosa. This was dominated by sheets of mature polymorphonuclear eosinophils which split the muscle bundles of the muscularis and surrounded the periarterial connective tissue. These cells usually extended into the deep submucosa and serosa. Less often, macrophages or giant cells were noted. The edematous areas consisted of a proteinaceous coagulum. Muscle areas at times appeared necrotic and varying degrees of hyalinization or replacement fibrosis were noted. True hypertrophy of the muscularis propria was common; hyperplasia only occasionally was seen. The mucosa was notably free of involvement except for a rare superficial erosion. There was nothing to suggest a granuloma.

Group B. Monoenteric Type (two patients). Pathology: Grossly and microscopically there was the same disseminated involvement seen in Group A. This extended from the pylorus in a retrograde manner involving the entire stomach rather than proceeding beyond to involve small bowel. One patient (Case 13) showed evidence of a more significant degree of periangitis.

Group C. Regional Type (thirteen patients including J. C. the patient reported on herein). Pathology (Table II): Here we have a more confined process limited to a particular region (usually prepyloric and pylorus) with ill defined borders. In one patient (Case 14) there appeared to be regional involvement over the entire small bowel; however, only gastric tissue was studied. The gross and microscopic picture was similar to those described previously, with certain modifications. There was less tendency for extension into the neighboring bowel structures. Lymphadenopathy was rare. The eosinophilic infiltration of the perivascular connective tissue appeared more marked, with fibrinoid necrosis and endarteritis. The infiltrative process often was more acute in that polymorphonuclear leukocytes were noted in the cellular infiltrate of some cases. In others, fibroblastic proliferation was more marked; in our patient (J. C.) we saw the early suggestions of a granulomatous process, with histiocytes.

Clinical Features of Class I Disease. The predominant age range in these three groups was the second to the fifth decade. There were fifteen males and ten females; the former predominated in group C, the latter in groups A and B. Eighty per cent had a significant history of gastrointestinal disorders recurring over a period of one to twenty-five years. These were principally intermittent episodes of severe nausea, vomiting, flatulence and diarrhea, with epigastric cramps and "heart burn" not relieved by antacids. In several instances there was a history of melena or hematemesis in the past. The illness leading to hospital admission and operation was usually a recurrence of previous symptoms, but more severe, painful and unremitting. Pyloric obstruction was observed in all but one of the polyenteric and monoenteric types (group A and B) and more than half of the cases in the regional type (group C). Cholecystitis and cholelithiasis were frequently noted on exploration (six patients).

An allergic history and symptoms appeared to be significant in about half of group A and B, asthmatic breathing being noted in five cases on admission. Four of twelve patients in Group C had an allergic history, and asthma was present in two of these. One patient (Case 12) had findings consistent with a diagnosis of Loeffler's syndrome. Both of our patients (Cases 10, 25) have exhibited typical asthmatic auscultatory signs associated with eosinophilia at some time during their clinical course, although neither has had a previous history of asthma or any other allergic disorder. Gastrointestinal allergy was suspected in four cases, since exposure to the offending substances usually provoked symptoms. Fifty-five per cent of the entire class I (A, B and C) had no allergic history or manifestation.

Laboratory study centered about the prominent eosinophilia in the peripheral blood. These were always mature cells. Bone marrow studies revealed no evidence of dyscrasia. Stool examinations for ova and parasites had negative results. As a rule, polyenteric and monoenteric patients had pronounced eosinophilia on admission which would persist or recur months to years after surgery. In the regional group, eosinophilia was not usually present preoperatively but appeared after surgery in most instances, to a modest degree and less persistently.

Leukocytosis was common in both A and B groups, in contrast to group C. Hemoglobin and hematocrit values were normal except in the rare instance of severe hematemesis (Case 23).

Gastric analysis, when reported, gave variable results, the majority of patients having free

TABLE III

CIRCUMSCRIBED EOSINOPHILIC INFILTRATED GRANULOMA—REGIONAL TYPE (CLASS II)

Case No.	Age (yr.) and Sex	Location	Allergy	Eosinophil (%)	Gross Pathology	Predominant Layer	Lymph Nodes	Authors
1	66,M	Stomach	+	...	Cherry size, antrum	Submucosa	...	Kofler [20]
2	...	Stomach	...	...	Nodular mass, antrum	Submucosa	...	Kofler [20]
3	51,F	Stomach	−	...	Apple size, mid-wall	All layers	+	Dalicho 1951 [21]
4	47,M	Stomach	−	1(18)	Nut size, pylorus	Submucosa	...	Moxo et al. [22]
5	38,M	Stomach	+	6(12)	Circumscribed, mid-wall	Submucosa	...	Frank [23]
6	44,M	Stomach	−	1	Tangerine size, lesser curvature	Submucosa	...	Picard et al. [24]
7	45,M	Stomach	−	...	Nut size, lesser curvature	Submucosa	...	Tavernari [25]
8	43,M	Stomach	−	10	Nut size, lesser curvature	Submucosa	...	Vangelista [26]
9	55,F	Stomach	...	...	Pigeon egg size	Submucosa	...	Distefano [27]
10	65,F	Stomach	−	...	Walnut size, prepyloric	Submucosa	...	Knezevic et al. [28]
11	23,F	Stomach	...	...	Egg size, greater curvature	...	...	Trincao [29]
12	40,F	Stomach	+	10	5 by 4 cm. mass, antrum	All layers	...	Cantor [30]
13	76,M	Jejunum	?	3	Orange size, annular	All layers	+	Polayes and Krieger [31]
14	55,F	Jejunum	...	Negative	6 by 2.5 cm. mass, occluding	Submucosa	...	Unnewehr and Ohrt [32]
15	62,M	Ileum	−	Negative	4 cm. oval mass, obstructing	Submucosa, muscularis	...	Urban et al. [33]
16	57,F	Ileum	−	...	Walnut size	Submucosa	...	Marek [34]
17	45,F	Ileum	−	20	Obstructing and ulcerating	Muscularis, serosa	+	Virshup and Mandelberg [34]
18	18,F	Cecum	−	...	Orange size	Submucosa	+	DeSantis [36]
19	42,F	Cecum	−	Negative	Orange size	All layers	...	Pezzoli and Reggiani [37]
20	64,M	Cecum	−	...	5 by 6 cm. mass	Submucosa	+	Picard et al. [24]
21	43,F	Colon	...	2	7 cm. mass, obstructing	Submucosa	...	Pardo and Rodriguez [38]
22	55,F	Rectum	...	10	Prune size	Submucosa	...	Steger and Noto [39]

acid present. Liver function tests were within normal limits. There was an unexplained fall in blood amylases in one of our patients (Case 10).

Roentgenographic study of the gastrointestinal tract revealed a striking picture in most instances. The stomach exhibited a smooth concentric narrowing of the antrum, suggesting an extrinsic mass or an infiltrating carcinoma. Peristalsis in the involved area was absent or depressed. Incomplete pyloric obstruction with fluid retention lasting hours to days was common. The duodenal bulb was frequently dilated, with tubular segmental narrowing in the small bowel (polyenteric group) interspersed with dilated loops. During periods of remission, these findings sometimes regressed.

Treatment in nineteen patients consisted of subtotal gastrectomy. In six of these there was difficulty in performing the anastomosis due to edema and friability of the stomach or bowel wall; however, there was no apparent difficulty in healing. In three patients gastroenterostomy was performed. A biopsy was obtained in three patients; in one instance (Case 1) the stomach was inspected grossly and an ileocolostomy was performed despite a severely involved ileum.

In three cases, including our own, corticotropin (ACTH) was administered after the diagnosis was established surgically. This drug was used to treat recurrences, with prompt subsidence of the symptomology and eosinophilia. An exploratory laparotomy for adhesions in one of these patients (Case 5) showed complete resolution of the pathologic process on gross examination.

Several recurrences in one of our patients (Case 10) were treated with the administration of oral corticosteroids. There was a prompt favorable response on each occasion.

Although it was notable in the polyenteric group that recurrences were more frequent and severe, the prognosis was good. Indeed, in our case the recurrences were acute and debilitating, and would require major surgical intervention were it not for the dramatic response to corticosteroid therapy.

Class II. Circumscribed Eosinophilic Infiltrated Granuloma

Group A. Regional Type (twenty-two patients). Pathology (Table III): This group was characterized by a circumscribed pseudotumor measuring from 1 to 10 cm. in diameter, located in any region of the gastrointestinal tract and disposed principally in the submucosal layer with occasional extensions to the muscularis and serosa. The mass was firm, often ulcerating and usually obstructed the lumen when the bowel was involved. Mesenteric involvement was rare but lymphadenopathy was frequently seen.

Microscopically the picture was one of a granuloma abundant in reticular and fibroblastic proliferating elements, histiocytes and newly formed blood vessels. Lymphocytes and

plasma cells were common. In some cases necrotic areas with foreign body giant cells were noted. The most arresting feature, however, was the massive infiltration of mature eosinophils throughout the lesion. These split the muscularis mucosa and muscularis propria in a manner noted in the previous section. The mucosa was more commonly infiltrated and ulcerated than in class I cases.

Clinical Features of Group A Disease. The age incidence in this group tended towards the fourth to sixth decades. The male/female ratio was about even. The clinical picture in general was less acute and a past history of gastrointestinal complaints less evident. The typical history was one of epigastric or abdominal crampy pain for several days or months. Vomiting and diarrhea were infrequent as compared with the disease in class I and overt allergy did not appear to be a prominent feature of this group.

Eosinophilia in the peripheral blood was usually absent, although one patient (Case 17) had 20 per cent eosinophilia, three had 10 per cent eosinophilia (Cases 8, 12 and 22) and in two instances the eosinophil count rose to 12 and 18 per cent (Cases 4 and 5) postoperatively. Leukocytosis was absent. Thus the blood picture was usually non-contributory although in a few instances similar to the regional cases of Class I. The roentgenographic signs were those of a neoplasm with little else to arouse ones suspicion as compared with that of diffuse eosinophilic disease.

The treatment, thus far, has been surgical removal in all cases reported. The prognosis is excellent, recurrences having been noted in only one patient (Case 22) involving the rectum.

Group B. Polypoid Type. This is the most commonly encountered eosinophilic infiltrated granuloma of the gastrointestinal tract. Over fifty cases have been reported in the literature [*18,20,40,51*].

Pathology: In general these lesions were firm, smooth, sessile or pedunculated polyps, often ulcerated, located at or near the pyloric antrum or more rarely along the small bowel [*18,20*]. In the stomach they were sometimes found in association with a peptic ulcer [*40*]. Rarely, they were large enough to prolapse through the pyloric canal, leading to pyloric obstruction [*41,42*].

The microscopic picture consisted of a granuloma with loose collagenous cells and intense infiltrate of eosinophils which extended from the submucosa to the mucosa. Histiocytes were less in evidence than in the class IIA type.

Clinical Features of Group B. As in the previous group the age range tended more toward the fifth to sixth decades, with no sex preference. The history was usually brief, with "ulcer like" symptoms, hemorrhage often being the only indication of disease. Allergic signs or symptoms were usually absent.

There was no peripheral blood eosinophilia. Gastric analysis frequently showed absence of free acid.

The radiographic picture was quite typical in most instances, revealing a sharply defined filling defect in the pyloric antrum. This defect was sometimes lobulated, the antrum being flexible with no interference of peristaltic waves. Treatment has been surgical. Recurrences have not been reported.

CASE REPORTS

Case 1. L. A., a forty-seven year old housewife with diffuse eosinophilic gastroenteritis-polyenteric type disease, was first admitted to the Genesee Hospital on November 12, 1955. The patient had a six week history of sharp intermittent crampy epigastric pain radiating through to the back, worse at night, with postprandial bloating and burning substernally not relieved by milk or antacids. One year before she had been hospitalized at another hospital for two weeks for similar symptoms and was told she had "stomach spasms." She continued to have recurrent upper gastrointestinal discomfort characterized by subxyphoid and high epigastric pain often precipitated by swallowing food. She complained of frequent eructations. A preadmission oral cholecystogram revealed a normal appearing gallbladder, and the upper gastrointestinal series demonstrated no intrinsic lesion although peristalses were peculiarly sluggish throughout. No ulcer or neoplasm was seen. The patient had been a mild diabetic for four years; her diet was well controlled. She was taking 15 units of protamine zinc insulin daily. Her remaining past history and family history were non-contributory. There was no history of allergy.

Physical examination, blood smear, differential count, sedimentation rate and urine analysis were non-contributory. She had 14 units of free gastric acid after the administration of histamine. She improved on a bland diet and antacid therapy and was discharged.

On September 2, 1959, she was readmitted. The patient had done well until August 1959, at which time she began to note intermittent mid-abdominal pain, some difficulty in swallowing food, and progressive postprandial nausea, bloating and belching. One

day prior to admission she had some "black" vomitus and felt that her "stomach was blowing up." Her diabetes had remained under good control on chlorpropamide, 250 mg. a day, for four months.

Physical examination revealed an obese woman with moderate abdominal distress. The pulse was 92 beats per minute and regular, the blood pressure was 126 mm. Hg systolic and 80 diastolic, the temperature was 100.4°F. rectally. There was a rasping cough associated with coarse rhonchi heard bilaterally and a distinct expiratory asthmatic wheeze. The remainder of her physical examination had negative results except for epigastric tenderness. No masses were palpable.

The urine specific gravity was 1.026, acid, and negative for sugar, albumin or significant sediment. The blood hematocrit was 43 per cent; the hemoglobin 14.2 gm. per cent. The leukocyte count was 25,600 per cu. mm.; the blood smear revealed neutrophils 45 per cent, band forms 4, basophils 2 per cent, lymphocytes 25 per cent, monocytes 2 per cent and eosinophils 22 per cent. Platelets were adequate. The sedimentation rate was 26 mm. per hour corrected (Wintrobe). Stools were negative for blood, ova and parasites. Liver function tests were all within normal limits and electrolytes remained stable throughout her course although there were traces of acetone in the urine. The serum amylase was unaccountably low on two occasions (16 and 26 units), but returned to normal following surgery. Leucine aminopeptidase was 24 units (normal, 10 to 20 units). Cultures of the nose and throat revealed mixed flora of non-hemolytic staphylococcus albus and streptococci, Neisseria catarrhalis and rare Diplococcus pneumoniae. Nasal smears for eosinophils were negative. The serum total protein was 7.2 gm. per cent. Protein electrophoresis was normal. Gastrointestinal roentgenogram showed a persistent localized contraction of the stomach 5 cm. proximal to the pylorus, circular in nature, maximum distention at this point being 3.5 cm. Contractions were more marked at times but never expanded outward. Mid-body peristaltic waves were interrupted but resumed in the more distal portion and carried on to the pylorus. The impression was one of a fibrous ring around the stomach. The duodenal cap appeared normal.

In view of the mild fever, leukocytosis, eosinophilia, cough and asthmatic breathing, the diagnosis of Loeffler's pneumonia was entertained along with some associated upper gastrointestinal disorder; however, serial roentgenographic examinations of the chest revealed no abnormal findings. The leukocytosis continued and the eosinophilia increased to 34 and 52 per cent. All cells were mature. Intravenous fluid therapy was started because of increasing abdominal distress and vomiting. Attempts at oral fluid feeding after a week of nasogastric suction failed and it was concluded that the patient had developed increasing pyloric obstruction. This was confirmed radiographically and she was explored.

At operation on September 16, 1959, free fluid was present in the peritoneal cavity. The liver and gallbladder were normal. There was a firm thickened mass in the lower third of the stomach extending throughout the duodenum and including approximately 15 feet of the jejunum. This presented a discolored surface not unlike that seen in regional enteritis. The pyloric ring was hypertrophied and occluded the lumen. Gastric resection and gastrojejunostomy was performed and a jejunal biopsy taken. The anastomosis was made in an area of the jejunum which appeared to be only moderately involved. No difficulty was encountered. The patient made a smooth and uneventful recovery. Her eosinophils decreased to zero twenty-four hours after surgery and rose slowly to 12 and 17 per cent on the fifth and twelfth postoperative day. She began taking fluids readily on the fifth day, and upon discharge two weeks later she was eating a normal diet without symptoms.

The pathologic specimen consisted of a subtotally resected stomach with attached 2.5 cm. duodenal cuff, measuring 19 cm. along the greater curvature and 10 cm. along the lesser curvature. The segment of the greater omentum attached along the greater curvature was soft, yellow, and contained no enlarged lymph nodes. The serosal surface of the stomach was soft, tan and glistening. The gastric wall varied in thickness measuring 1.7 cm. in the pyloric region, 1.2 cm. in the antrum, and 0.8 cm. in the proximal portion of the specimen. The thickness of the wall in the pyloric and antral region was apparently due to hypertrophy of the pyloric muscle, which extended in a spindle-shaped fashion into the antrum, being greatest at the pylorus where it measured 1.1 cm. in thickness and gradually decreasing proximally until it averaged 0.7 cm. in the antrum. The subserosa was edematous throughout the specimen and averaged 0.2 cm. in thickness. The mucosa in the antral region presented a granular pebbled appearance, due to nodular thickened areas. The rugal pattern was absent in this region and a few superficial erosions were present, the largest measuring 0.7 cm. in diameter. In the proximal portion of the specimen the mucosal folds were moderately prominent, pliable and broadened. The mucosa was slightly granular and mottled by petechial and confluent recent, superficial hemorrhages.

Microscopic study of multiple sections through the pyloric and antral regions of the stomach showed thickening of the wall due to edema, fibrosis and diffuse cellular infiltration of the submucosa, muscularis and subserosa. The predominant cells in the latter process were eosinophilic polymorphonuclear leukocytes. These cells were aggregated in great numbers chiefly in the muscle layers and frequently formed solid masses and columns. A moderate

number of neutrophilic leukocytes were also seen. Lymphocytes and plasma cells were infrequent. Histiocytes, particularly those of xanthomatous character, were not encountered. Degenerating muscle fibers and proliferating capillaries and fibroblasts were present in and around the eosinophilic infiltrate. The process of tissue eosinophilia extended up to the subserosal fat but did not involve it. The submucosa was involved focally. Congestion, focal hemorrhage and focal chronic inflammation and scarring marked the serosal surfaces. Frank necrosis of the tissue was not found; tubercles, abscesses and foreign body particles or neoplastic cells were not encountered. The muscularis mucosa was well preserved. The mucosa was edematous, focally hemorrhagic and marked by frequent lymphocytic aggregates. Atrophy of the gastric glands was present in some fields. Zones of young fibrous tissue proliferated in the submucosa and subserosa around the pylorus. Serositis with adhesions was evident in some areas.

The specimen of the jejunal biopsy consisted of a 2.5 by 0.8 cm. piece of jejunum from the site of anastomosis. Microscopic sections showed a diffuse process similar to that previously described. There was edema of the submucosa and a widespread eosinophilic infiltrate in the submucosa, muscularis and subserosal layers, accompanied by moderate numbers of proliferating capillaries, fibroblasts and polymorphonuclear leukocytes.

On October 17, 1959, she was admitted for the third time. One week following discharge the patient began to develop recurrent symptoms similar to those of her previous admission, with increasing nausea and vomiting. Pain was periumbilical and colicky in nature. Examination revealed guarding in the left upper quadrant of the abdomen, diffuse upper abdominal tenderness and hyperactive bowel sounds. Routine laboratory studies were within normal limits except for a 19 per cent eosinophilia observed in the blood differential count. Upper gastrointestinal roentgenograms revealed delay in emptying at the anastomotic site but no organic lesion. There was segmentation of the small bowel pattern.

It was suspected that the obstructive features were due to the diffuse eosinophilic infiltrative process in the jejunal anastomosis and the patient was started on a regimen of Acthar Gel® (corticotropin) 40 units every eight hours on the fourth hospital day. This was gradually decreased to 20 units per day by the eleventh hospital day. Within forty-eight hours following the administration of ACTH the patient began to show improvement and by the time of discharge on October 28, 1959, all corticosteroid therapy had been discontinued. She was eating a full diet and was asymptomatic. Her eosinophilia decreased to zero and remained there. A repeat upper gastrointestinal series before discharge showed some slight delay in emptying with improvement over the previous study. Repeated attacks during the following six months were treated with oral corticosteroids with prompt remission of symptoms on each occasion.

Case II. J. C., a thirty-one year old white married male laborer with diffuse eosinophilic gastroenteritis-regional type disease, was admitted to a neighboring hospital in February 1950. He had severe abdominal pain and vomited for several hours. He appeared acutely ill and dehydrated. His past history revealed frequent recurrent episodes of upper abdominal distress associated with vomiting of two to three days' duration, unrelated to foods and not relieved by antacids. Because of persistent symptoms nasogastric suction was performed for ten days. Several attempts to complete upper gastrointestinal roentgenographic study during this period were inadequate because barium could not pass through the pylorus. On the tenth hospital day a barium meal was observed during a five hour period. There was active peristalsis, the pylorus was well formed, with a dilated duodenal cap which retained barium for several hours, and "dumping" into the small bowel where a diverticulum was noted.

Blood studies were normal on admission. The leukocyte count was 10,250 and 8,750 cells per cu. mm. There were 9 per cent eosinophils in two peripheral blood smears.

Because he continued to have symptoms and signs of a high obstruction, subtotal gastrectomy was performed. At operation the liver appeared normal and palpation of the stomach was normal except for a thickened pylorus, the lumen of which was narrowed, permitting only the tip of the finger to be passed. The duodenal cap and descending portion of the duodenum were rolled over and pulled to the underside of the liver by strong peritoneal bands. A considerable degree of vascularity was encountered in the region of the ampulla where a diverticulum was seen. Enlarged reddened mesenteric nodes of the small bowel were noted. Cholecystostomy was performed at this time because of a tense abnormal looking gallbladder.

The pathologic specimen of the stomach was 13 cm.; there was marked hypertrophy of the pylorus, which measured 1 cm. in diameter, forming a constricting ring. There was hypertrophy of the prepyloric muscle which measured 5 mm. The gastric rugae were normal and the serosal surface was smooth. Sections throughout the pars pylorica of the stomach showed a diffuse thickening of the gastric wall due to hypertrophy of the pyloric muscle, edema of the submucosa and the presence of an inflammatory lesion of granulomatous character. The latter involved chiefly the submucosal layer and was composed of numerous capillaries and small blood vessels, and a dense network of collagenous fibrils, infiltrated by eosinophils, leukocytes, occasional lymphocytes and histiocytes. Among the cellular elements the eosinophils were by far the dominating cells, densely accumulated in some areas, sparse in other fields where collagen fibers prevailed. The muscularis mucosa was generally well

preserved, showing the normal parallel arrangement and only occasionally involved by the cellular infiltrate. The overlying gastric mucosa was intact and thrown into prominent folds. Active ulcers were not found. The lamina propria was not extensively infiltrated by inflammatory cells, although occasional lymphoid aggregates occurred and there was loose scattering of eosinophils and neutrophils. The inflammatory process extended into the muscularis, penetrating between the muscle bundles. Aggregations and nests of eosinophils, occasional lymphocytes and histiocytes, supported by collagen fibrils and blood vessels were seen within the muscle layers. In places these changes extended throughout the full thickness of muscle, elsewhere they were focal and less extensive. Infiltrates of eosinophils and neutrophils were constantly seen around the nerves and ganglia between the muscle layers. The vascular channels were congested and the lymphatics were dilated and contained clear lymph. In some areas the subserosa was infiltrated by eosinophils and neutrophils and showed mild increase in collagen fibrils, but was otherwise non-contributory. The omental fat contained congested blood vessels and dilated lymphatics and small arteries with thick walls, but lacked other evidence of sclerosis. A short strip of postpyloric duodenal mucosa was marked chiefly by edema and lymphocytic infiltrates on the surface epithelial structures. Eosinophilic infiltrates were noted in the underlying muscular layers.

Postoperatively the patient did well. The leukocyte count remained within normal limits; however, eosinophils in the peripheral blood rose to 16 per cent within two weeks.

Fourteen months after surgery he had two recurrences of crampy abdominal pain with vomiting and diarrhea. During these episodes he had an elevated leukocyte count and 15 per cent eosinophilia on one occasion, although subsequent blood smears were normal. In February 1955 he was admitted to the Genesee Hospital for a cholecystectomy because of periodic epigastric distress, fried and fatty food intolerance, and a cholecystogram which revealed no concentration of the dye. Bronchial wheezing was noted on admission but no eosinophilia.

Pathologic examination of the gallbladder revealed acute and chronic cholecystitis with granular proliferation. A moderate number of lymphocytes and eosinophils were noted in the lamina propria.

Blood studies on this admission were within normal limits. The patient's postoperative course was uneventful and his infrequent epigastric distress was controlled by antacids, antispasmodics and a bland diet.

He was readmitted in April 1958 for a febrile illness with acute right upper quadrant abdominal pain, at which time a subhepatic abscess was drained surgically. At this time numerous blood smears revealed only an occasional mild eosinophilia bone marrow study, and stools for ova and parasites were negative.

His most recent admission was in November 1959 because of an acute upper respiratory infection associated with a pronounced asthmatic wheeze. Culture of the sputum grew no pathologic organisms. A roentgenogram of the chest revealed no abnormalities. The blood smear revealed an eosinophilia of 23 and 24 per cent. He made a good recovery on conservative treatment and has been well since except for his recurrent diarrhea and epigastric distress.

COMMENTS

Although these cases may be separated into groups with distinguishing pathologic and clinical characteristics, there is of course the possibility that they may have a common etiology, representing somewhat different biologic expressions of the same process. Koch [*47*] suggests that the varying histopathologic pictures described by some authors may reflect different chronologic stages of the lesion.

Both patients of Ferrier and Davis [*8*], Orr and Miller [*5*] were noted to have progressive involvement as well as extension of this disease to other areas when re-explored surgically after an interval of several years. It is probable, therefore, that diffuse monoenteric disease may at times become polyenteric, and that some regional types may also extend in time.

The eosinophil is a normal component of gastrointestinal tissue [*52*] and is observed in increasing concentrations in such diverse pathologic states as Hodgkin's disease [*53*], gastrointestinal carcinoma [*58*], amebiasis [*59*], helminthic disease [*60*] and gastric ulcers [*61*]. The concentration of eosinophils observed in the cases under consideration is of an order that places them apart from other pathologic states. Here the cells concentrate in large masses or sheets that infiltrate the affected layers. Although they may at times be focally situated about blood vessels, lymphatics or ganglia, for the most part they swarm over tissue in a homogenous distribution. How then may we explain this intense cellular reaction?

Blood and tissue eosinophilia are the common accompaniments of antigen-antibody activity, although not dependent upon active antibody formation [*62*]. It is not known why the shock tissues have a special affinity for eosinophils "unless they are the transporters of antigen to these sites or the antigen present there transforms other types of cells in these tissues into eosinophils" [*66*].

It is difficult not to conclude that we are dealing with some form of hypersensitivity reaction.

In support of this we have the frequent observations of plasma cells interspersed throughout the involved areas. These are recognized as being intimately concerned with the elaboration of antibodies [*67*]. The prevalence of periarterial and perivenous infiltration, the less frequent fibrinoid necrosis and endarteritis are all consistent with a hypersensitivity phenomenon.

Many authors placed eosinophilic gastrointestinal disorders under the broad category of allergic disorders. Ruzic et al. [*11*] called his case the "gastric lesion of Loeffler's syndrome" based on previous pulmonary findings and eosinophilia. He was influenced by reports in which pleural, pericardial and peritoneal involvement were described in patients with typical Loeffler's syndrome [*63,64*] and by Bergstrand's [*65*] concept of rheumatoid arthritis, periarteritis nodosa, rheumatic carditis, and transient lung infiltration with eosinophilia as equivalent manifestations of an antigen-antibody reaction localized to different organs. Asthmatic breathing, cough, fever and eosinophilia were noted in both of our cases at some time during their clinical course; however, roentgenographic studies of the chest repeatedly revealed no abnormalities. Swarts [*1*] includes eosinophilic peritonitis among the eosinophilic gastroenteritides and favors Ruzic's concept. McCune [*12*] places great emphasis on the evidences of vasculitis. Houghton [*19*] classifies his case as a gastric lesion of disseminated eosinophilic collagenosis. This derives from the description detailed by Bousser [*68*] of a syndrome which may concentrate in any organ, always in the presence of eosinophilia, with a variable course progressing to recovery or death depending on the degree of vascular infiltrative involvement.

Whether or not we are dealing with an allergic mechanism certain statements can be made in reference to patients with class I disease. (1) There is commonly a history of allergy, particularly of asthma. (2) A history of acute or chronic allergy may be completely absent. (3) The severity of the disease is not related to the presence of a history of previous allergic disease. (4) The antrum and pylorus are the most frequently involved structures. (5) Patients with more profound and persistent eosinophilia have more extensive bowel involvement. (6) The "factors" provoking the blood response persist or recur in both polyenteric and monoenteric patients, and appear to stimulate eosinophilia after surgical removal of the lesion in regional cases (and even some circumscribed cases).

An unanswered question revolves about the relationship of class I and class II disease. We have avoided the term "eosinophilic granuloma" since the pathology in this disorder is to some extent different. Vanek [*40*] stresses that polypoid lesions do not have histiocytes or reticular cells and that the eosinophils are not densely accumulated focally but are homogeneous. Lipoid phagocytosis and foam cells are absent. This is in contrast to the classic description of eosinophilic granuloma of the bone by Lichtenstein and Jaffe [*56*]. Subsequent reports by other authors (Table III) have noted the presence of histiocytes and focal arrangement of eosinophils in some layers. The presence of histiocytes in our second case (J. C., class IC), although most unusual in the diffuse type, suggests a connecting link between class I and class II gastrointestinal disease. The presence of a regional diffuse lesion in combination with two eosinophilic infiltrated polyps in Van der Linden's case [*18*] supports this possibility.

The almost total absence of peripheral blood eosinophilia in the circumscribed group and the lack of a prominent allergic history has focused attention on possible local inciting agents. Inflammatory granulomas have been produced experimentally by Sherman and Moran [*55*] who injected various substances, including gastric juice, into the stomach wall of rabbits. They also reported six chronic granulomas of the stomach, all of which they regarded as "foreign body type." Two occurred in response to ingested food particles, the others around peculiar eosinophilic or faintly basophilic material believed to represent degenerated masses of smooth muscle or fibrous tissue arising from the digestive action of gastric juice which penetrated the mucosa. In all but one of these patients the disease was associated with a peptic ulcer [*54*].

Finally, a word must be said about therapy. Surgery in patients with class I disease has usually been life saving, although recurrences have been frequent; no deaths have been reported to date. Nevertheless, it is obvious that the surgeon cannot remove the affected tissues entirely in most cases of this disease. In class II disorders surgery is definitive, and recurrences are almost non-existent.

ACTH and corticosteroids have been shown to induce striking remissions in class I lesions and it is possible that many patients in the future will be diagnosed and treated without surgical intervention, using corticosteroids as the sole

modality. Whether or not class II patients will respond in a like manner remains to be seen. True eosinophilic granuloma of the bone has been reported to clear completely with ACTH [*57*]. It is disturbing to find that adrenal steroids were not effective in cases of eosinophilic peritonitis reported by Harley [*69*].

The ultimate treatment resides in a clearer understanding of the cause or causes of this unusual group of gastrointestinal disorders.

SUMMARY

A classification is proposed for idiopathic eosinophilic infiltrations of the gastrointestinal tract, based on pathologic, clinical and laboratory features. Two relevant cases are added to the literature.

In general, patients with a long-standing history of upper gastrointestinal complaints, with or without overt allergies, a roentgenographic picture of a constricting antrum or pylorus, and/or segmental narrowing and dilatation of the small bowel, associated with eosinophilia and leukocytosis, have diffuse eosinophilic gastroenteritis of the monoenteric or polyenteric type. The evidence suggests that these patients can be treated successfully with adrenocortical steroids and that surgery may be avoided.

The regional type of this disease is confined for the most part to the pyloric area, causing obstruction in the absence of peptic ulcer, with little in the peripheral blood to aid in the diagnosis.

Circumscribed eosinophilic infiltrated granulomas are well demarcated lesions of the regional or polypoid type, occurring anywhere in the gastrointestinal tract, giving local signs, and easily confused with neoplasm.

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Reviews

Correlation of Radioactive and Chemical Fecal Fat Determinations in the Malabsorption Syndrome*

I. Studies in Normal Man and in Functional Disorders of the Gastrointestinal Tract

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Many methods of studying fat absorption from the gastrointestinal tract have been used. A time honored procedure is the gross and microscopic examination of the stool. While of value in overt steatorrhea this method is only qualitative at best and often misleading since a considerable amount of fat may be present but not demonstrable in this way. Vitamin A and carotene levels have been advocated as indices of fat absorption but have not gained wide popularity because of the technical difficulties of the determinations. Chemical analysis of the plasma for lipids presents technical problems usually requiring the facilities of a research laboratory. Plasma turbidity and chylomicron counts have been advocated but, because of many variables involved, have limited usefulness. The analysis of aspirated intestinal contents after ingestion of a known test meal is a direct method but is time consuming and somewhat uncomfortable. Fecal balance technics, with chemical determination of fat and nitrogen, are thought to be the most accurate method of assaying assimilation. However, these fat balance studies are time consuming, laborious and expensive and require the facilities of a metabolic ward and three to five days for collection of stools.

The use of tagged fat or oil as a test substance to evaluate fat absorption has been reported in the literature from time to time. The development of isotopes and their popularity as a means of labeling compounds has resulted in a number of studies utilizing fat tagged with radioactive iodine (I^{131}). These tests are relatively easy to perform and can be carried out in any radioisotope laboratory. It is the purpose of this investigation to compare the accuracy of radioactive I^{131}-labeled triolein studies with chemical fat and nitrogen balance examinations of the stools as diagnostic aids in the various malabsorption syndromes.

REVIEW OF LITERATURE

Origin of Fecal Fat. Investigations of the origin of fat in the feces of normal man have resulted in conflicting views on whether such fat is derived mainly from endogenous sources or from unabsorbed dietary fat.

It is generally agreed that bacterial synthesis, desquamated cells of the intestine, and bile contribute a small proportion of the total amount of fat. Norcia and Lundberg [*36*] consider that endogenous fat is derived from bacterial synthesis, a view that receives some support from the occasional response of patients with steatorrhea to the oral administration of antibacterials [*20–24*]. The studies of Bloor and Sperry [*11,27,*

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48–51] suggested that the fecal lipid was to a large extent derived from excreted material rather than from unabsorbed dietary fat. This hypothesis was based on their observation that changes in the amount and character of lipid in the food did not influence the amount or composition of the fecal lipids. Wollaeger et al. [*60*] showed that as fat intake increased fecal fat content also increased. An increase in the dietary fat intake of up to 350 gm. per day resulted in significantly increased amounts of fat in the feces. From this they concluded that dietary fat was the major factor in determining the amount of fat in the feces in normal persons.

Annegers et al. [*3*] investigated the relationship between fat intake and fecal fat excretion in a study in which forty subjects were given two types of fat at three quantity levels, the daily caloric intake remaining at 3,000 calories. From these experiments they concluded that variations in the type or level of the dietary fat intake from 93 to 150 gm. per day did not appreciably influence the amount of fat in the feces of forty normal subjects. This indicated that fat balance, "digestibility" studies were of questionable validity since within the ordinary dietary limits fecal fat excretion is independent of dietary fat intake when lard and hydrogenated vegetable oils were used. Also the free fatty acid content and iodine number of fecal fat differed from those of the dietary fat in ten subjects, indicating that fecal fat is not an undigested residue of dietary fat.

Cook [*11*], after reviewing the available evidence on the source of fecal lipids in normal subjects, concluded that the greater part of the fecal lipid was secreted by the intestinal wall. He based this conclusion on the evidence that the fecal lipid was relatively constant in amount and composition, and that the intestine is known to be metabolically active in the synthesis of lipids, including cholesterol.

A study of three persons with presumably normal absorption who received fat-free diets was reported by Lewis and Partin [*33*]. The average amount of lipid in the feces was 2 gm. per day, which the authors interpreted as being evidence for the intestinal secretion of lipids.

In 1950 Weijers and Van de Kamer [*58*] showed that in patients with celiac disease there appeared to be either a specific failure to absorb saturated fatty acids or excretion of saturated fatty acids in excess of the dietary intake. The latter explanation was preferred by Weijers and Van de Kamer [*57*] as they showed that children with celiac disease maintained on a diet containing gluten, but no fat, passed 6 to 10 gm. per day of saturated fatty acids in their feces, suggesting excessive endogenous production.

The question of diet and fecal fat excretion in patients with sprue was studied by Asenjo et al. [*4*]. When these patients received a test diet that supplied 90 to 95 gm. per day of easily digestible fats (actual intake about 80 gm.) their fecal fat excretion was increased. When the fat intake was reduced to 10 gm. per day, the steatorrhea disappeared and the daily fat excretion was within the range of normal.

Comfort et al. [*13*], in another study of patients with the sprue syndrome, showed that raising the fat intake from 50 to 100 gm. per day increased but did not double the fat in the feces. Any defect which prevents normal absorption of dietary fat may also prevent normal reabsorption of fat from the bile and other endogenous sources, leading to an increased amount of fat in the feces [*23*].

Crowe et al. [*17*], after performing complete and partial balance studies on twelve and eighteen subjects, respectively, concluded that full balance studies are unnecessary for the detection of steatorrhea, and that estimation of the fat content of the feces gave a sufficiently reliable indication of steatorrhea.

Frazer [*20,21*] suggests that it is unwise to convert fecal fat figures into any coefficient of fat absorption. He prefers to express the results of fecal fat analysis on the factual basis of grams of fecal fat per day.

Fecal Balance Studies. In general, quantitative methods based on the excretion of fat in the stools require some form of fat balance. The full balance method is undoubtedly the best; both the diet and the stools are analyzed for fat content and the balance is determined over a period of three to six days. A weighed diet is given to the patient, an exact duplicate is kept for analysis. All diet residues are weighed, analyzed and subtracted from the duplicate diet. Carmine capsules are used to mark the stools at the beginning and at the end of the study period [*12*]. Some investigators [*22*] prefer to analyze twenty-four hour stool specimens so as to follow the daily fluctuations. This daily analysis obviously is more time consuming than a single analysis, and constipation may interfere with the daily collection of a stool for the twenty-four–

hour analysis but makes no difference if stool markers are used over a three- to four-day period.

A variation of the full balance method eliminates analysis of the diet by using food composition tables for the calculation of the fat content of the diets. A third variation of the balance method is often used in which patients receive an ordinary unweighed diet, the fat content of which will always be less than 150 gm. per day as long as excess fat is not taken and the stools are marked at the beginning and end of the study period of three to four days. This balance method is based on the observation that the amount of fat in the feces in normal subjects is relatively constant and independent of the dietary intake if not in excess of 150 gm. per day [*3,13,16,60*].

Chemical Determination of Fecal Fat. A very rough qualitative method for evaluating fat absorption is the microscopic examination of feces with the use of Sudan III as a staining agent. The accuracy of this method depends on the experience of the examiner and, although there is usually a high degree of correlation between the chemical balance studies and the microscopic gradings of 0 or 4 plus, the intermediate grades cannot be interpreted accurately [*1,30,54–57*].

The amount of fat in stool may be estimated in wet or dried feces. It has been held by those who use the wet feces that the process of drying may drive off some of the more volatile fats and that there may be some hydrolysis of neutral fat, thus giving rise to misleading information about the percentage splitting of the fats. The percentage of dry matter in feces is not necessarily constant, however, and may be quite variable in feces from patients with metabolic disorders or faulty absorption. Most workers [*15,22,23,54,59*] now agree that this is not an accurate method. Several technics have been used in this country [*19,42,48,49,53*]. The Fowweather [*19*] method, a modification of Saxon's, utilizes wet feces. Anderson [*1*] compared the Sperry method [*49*] with that of Fowweather and found the Sperry technic to be more reliable.

Most of the methods use ether to extract the fat. Van de Kamer et al. [*54*] showed that ether extracts not only fats but also ether-soluble nonfats, thus giving high estimates. They also described a rapid and convenient method which is particularly suited for use in connection with fat balance tests. The test is based on the principle that fatty acids and fat can be extracted almost quantitatively with petroleum ether from an acidic solution of about 60 per cent ethanol saturated with sodium chloride and containing a small amount of amyl alcohol. The results are expressed in terms of fatty acids. It is now generally agreed [*20–25,56*] that this is the method of choice. Moreover, this technic has an additional advantage. If liquid paraffin has been taken and is present in the feces, it will be extracted into the neutral fat by all of the methods except this one, in which it will not be titrated. Also, the technical error by this procedure does not exceed 2 per cent.

Radioactive Lipid Studies. The use of fat or oil tagged with a tracer element to evaluate fat absorption was reported as early as 1931, when the use of iodine-containing oil to study fat absorption was described in the German literature. Lipiodol was used by a group of French workers in 1931 and 1932 in the study of pancreatic insufficiency. Sicard and Forestier [*61*] also used lipiodol as a means of studying fat absorption. In the American literature, Groen reported on the use of this agent in 1948. He observed the disappearance of lipiodol radiologically from the gut and used this as an index for the absorption of fat. In addition he studied the excretion of iodine in stool and urine and used this as an index of fat metabolism. Lelong et al. used lipiodol as a test material for the diagnosis of fibrocystic disease of the pancreas. Silverman and Shunkey also reported on the use of lipiodol in the study of absorption of fat.

The availability of radioactive iodine (I^{131}) led to its early use as a label in metabolic fat studies. I^{131}-labeled olive oil was prepared by saturating the double bond of the constituent fatty acid, oleic acid, with radioactive iodine. Stanley and Thannhauser [*52*] measured the total radioactivity of the serum following a 5 gm. oral dose of 100 μc. of the labeled oil in eighteen human subjects. The serum lipids were coprecipitated with the plasma proteins, using Somogyi reagents, and the radioactivity measured. The values for total radioactivity minus the values for water-soluble activity were taken as the lipid activity, and were expressed as a percentage of the administered dose per 100 ml. The authors reported only slight differences between results obtained by this method of separating the serum lipids and by extraction of blood lipids with ether-alcohol solution. The activity of the thyroid gland and the activity excreted in the urine were also determined. The rate of

accumulation of activity from free inorganic iodide split off from the fatty acid molecule during metabolism was considered an index of the rate of utilization of the iodinated fat. From 15 to 48 per cent of the administered radioactive iodine was excreted in the urine of normal men in twenty-four hours, half of this being accounted for in the first six hours. The accumulation of radioactivity by the thyroid gland varied from 10 to 25 per cent of the administered dose in twenty-four hours. In ten normal subjects the concentration of total I^{131} in the serum was greatest at three to six hours following the meal and slowly decreased after this time.

Hoffman [*28*] demonstrated that I^{131}-labeled oleic acid was incorporated into adipose tissue of rabbits following its oral administration. McCandless and Zilversmit [*31*] demonstrated that I^{131}-labeled triolein, given intravenously as an emulsion, is handled in a manner quite similar to C^{14}-labeled tripalmitin. Van Handel and Zilversmit [*55*] investigated the character of the I^{131} label, particularly as to whether it follows the fate of carrier fat after intravenous and oral administration to dogs. When I^{131}-labeled triolein was mixed with cottonseed oil and injected as an emulsion, the I^{131}-labeled triolein disappeared at the same rate as the carrier fat. To investigate the effect of the gastrointestinal tract on the stability of I^{131}-labeled fat, alimentary lipemia was produced by feeding cottonseed oil mixed with I^{131}-labeled triolein. The appearance and disappearance of radioactive triglycerides in plasma agreed closely with that of the chemically determined triglycerides.

The radioactivity of the blood following ingestion of I^{131}-labeled fat, and its correlation with gastric emptying time in normal subjects, was studied by Baylin et al. [*5*]. Shingleton, Baylin, Wells, Ruffin and their associates [*5,6, 38–41,43–45*] have described the use of I^{131}-labeled triolein as a test material for the study of fat absorption in both animals and man. These authors concluded that the method is a simple, accurate and reliable test of fat absorption. For the usefulness of this test they set forth the following evidence: The radioactive material that appears initially in the blood cannot be dialyzed, indicating that I^{131} is attached to the fat, as ingested, or to a split product of digestion; electrophoresis of portal vein blood in animals showed that I^{131} is bound to beta lipoprotein and the neutral fat fraction. The radioiodine blood levels after a test meal with I^{131}-labeled fat are profoundly lowered in pancreatectomized dogs, whereas after the ingestion of I^{131} alone the blood levels were normal; a striking inverse relation exists between radioactive material in the blood and in the stool, a lowered blood level being invariably associated with an elevated fecal content and vice versa (this does not hold true in our experience, as well as that reported by Grossman et al. [*26*]). The radioactive material that appears in the stool cannot be dialyzed and on ether extraction was found in the fat fraction.

They also emphasized several other points; in the group of patients diagnosed as having functional gastrointestinal disturbances, the blood levels and fecal excretion were all within normal limits. On the other hand, patients who had disease of the small bowel, regardless of cause, invariably had a marked lowering of the blood levels and marked increase in radioactive content in the stool. Patients with disease limited to the colon had normal absorption. This was also true of patients with cirrhosis of the liver. The evidence in patients with disease of the pancreas pointed to faulty digestion rather than to an intrinsic error of absorption.

This test was further evaluated by Beres et al. [*7*] who measured the lipid bound I^{131} instead of the whole blood radioactivity. They confirmed most of the observations of the previous group, but believed that the urinary excretion of I^{131} provided less information than a study of the blood lipid I^{131}. It was their opinion that, although the fecal excretion of I^{131} was a satisfactory measure of fat absorption, it required a complete three-day collection of feces. They agreed, however, that the study of fat absorption with I^{131}-labeled triolein in man has been an extremely useful adjunct in evaluation of the malabsorptive diseases.

McKenna et al. [*35*], believe that, although the blood curve is a good indicator of the absorption rate, the I^{131} stool recovery gives a better estimate of the total absorption of the labeled fat.

Reemtsma, Malm and Barker [*37*] advocated for clinical use in the differential diagnosis of malabsorption states a simplified version of the test based on the percentage of the administered dose present in the blood stream at four hours.

Spencer and Mitchell [*47*] determined fecal excretion after the oral administration of I^{131}-labeled triolein in eleven patients with steatorrhea and in ten patients without steatorrhea. They concluded that the determination of fecal

radioactivity was easy to perform and economical, and could be performed on an outpatient basis.

Shoemaker and Wase [*46*] studied I^{131}-labeled triolein absorption in fifteen patients who had been subjected to high subtotal gastrectomy with gastroduodenal (Billroth I) anastomosis and in nine patients with Billroth II anastomosis. The patients in both of these groups, as well as ten and thirteen normal subjects, were studied with the small (3 ml.) as well as the load (63 ml.) tests. In normal subjects, after oral administration of the small dose, there was a gradual rise until a peak was reached at about four hours. The rise was more gradual with the larger dose and the average peak was not reached until about eight hours. After the small dose a more rapid initial rise occurred in both groups of postgastrectomy patients, although the values were somewhat greater for those who had been subjected to Billroth I anastomosis.

METHODS AND MATERIAL

Twenty-four volunteer subjects, members of the house-staff and laboratory personnel, were evaluated as normal control subjects. One hundred and two patients from the Gastrointestinal Service of the Graduate Hospital of the University of Pennsylvania were studied as malabsorption suspects. The clinical diagnoses in these 102 patients were as follows: idiopathic steatorrhea, ten; non-specific regional enteritis, twelve; disease of pancreas, twenty; diseases of hepatobiliary system, fifteen; functional enterocolonopathy, thirteen; gastric resections, eleven; nonspecific idiopathic ulcerative colitis, five; miscellaneous diagnoses, sixteen. The results in the normal volunteer subjects and in the patients with functional enterocolonopathy will be reviewed in this paper.

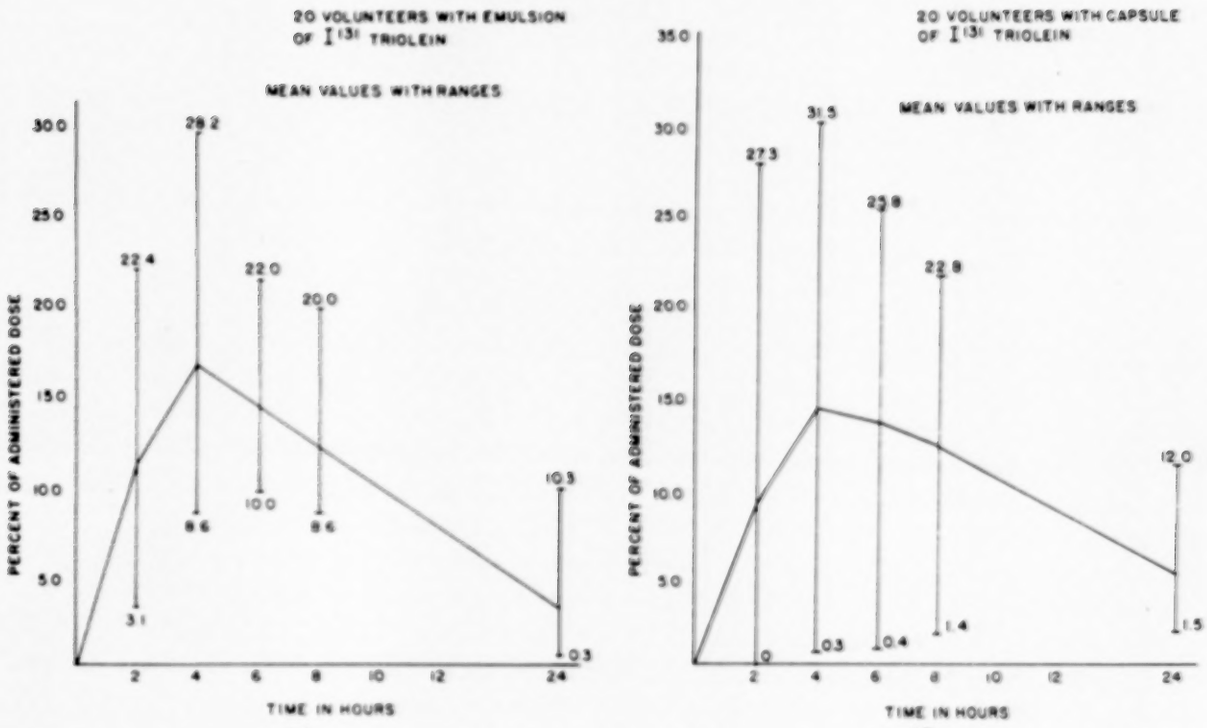
Diagnosis in these patients was based on history, physical examination and x-ray studies according to need, including one or all of the following: upper gastrointestinal series, small bowel barium progress meal, barium enema, cholecystography and splenoportography. In addition, the following laboratory studies were made on all subjects: hemogram, blood chemical studies, fasting blood sugar, blood urea nitrogen, serum proteins, prothrombin time, bromosulphalein retention test, cholesterol, amylase, lipase, bilirubin, serum calcium and electrolytes. In some special laboratory studies were made, such as glucose tolerance test, starch tolerance test, secretin test with cytology, gastric analysis and small bowel biopsy.

The patients and volunteer subjects were given a standard Schmidt type diet containing 100 gm. of fat, 120 gm. of protein and about 270 gm. of carbohydrate per day for about forty-eight hours prior to the test meal and during the balance study. In each instance it was established that the patient's dietary intake of fat was at least 50 gm. or more per day. All the food not consumed was returned to the diet kitchen for calculation.

I^{131}-Labeled Triolein Emulsion Meal. Each person was given 10 minims of Lugol's solution three times a day for two days prior to study to block the uptake of radioactive iodine by the thyroid gland. On the day of the test 20 gr. of carmine was given at 7 A.M. after the subject had been fasting from the previous midnight. About 8:30 A.M. the test meal was prepared, consisting of 25 to 100 μc. of I^{131}-labeled glycerol trioleate and 0.5 ml. of peanut oil per kg. of body weight, emulsified in an equal amount of water with 2 to 3 ml. of Tween 80. Barium sulfate (20 gm.) was added to the test meal and the ingredients were mixed in a Waring blendor. The meal was then transferred to a waterproof carton which was then assayed for its radioactivity content. Following ingestion of the meal the carton was rinsed several times, and the subject drank the rinse water. The carton was then reassayed for residual radioactivity so that the exact amount administered was known. About one to two hours after the test meal the subject was allowed to eat the Schmidt diet breakfast.

Seven milliliters of venous blood was withdrawn in a standard oxalated tube at two, four, six, eight, ten, twelve and twenty-four hours following the test meal. Each sample was assayed in a calibrated sodium iodide, thallium-activated scintillation crystal well counter. The total blood volume was calculated on the basis of body surface area (3,000 ml. per square meter of body surface area). Using the measured radioactivity of the blood sample and the calculated blood volume, the total radioactive blood level was determined and expressed as a percentage of the ingested material.

All stools passed during the next ninety-six or more hours were collected, taking care to keep the samples free of urine. If, after the test meal, the first stool specimen did not contain the carmine dye, this specimen was collected separately in a waterproof half pint carton. But if the dye did appear, the first specimen containing the dye and all subsequent specimens were collected in a wide-mouthed, previously weighed jar, which contained 100 ml. of concentrated hydrochloric acid. After the first carmine dye administered had been completely discharged, and the stool had returned to its original color, the second dose of carmine, 20 gr., was given at 7 A.M., usually on the fourth to seventh day. The stool specimen showing this second dose of carmine was collected in a waterproof carton. All stool samples (cartons as well as the jar) were assayed on the well counter for radioactivity. The stool collections were continued if the last specimen containing the second dose of carmine showed significant radioactivity; if there was no significant activity, the collection was



1A 1B

FIG. 1.

completed with this specimen. Corrections for counting were made by establishing standard curves, using a known amount of radioactivity and different volumes of homogenized solution in the cartons as well as in the jars. Direct comparison between the net sample counts per minute and the net standard counts per minute permitted estimation of the total radioactivity recovery in the feces as a percentage of the ingested material.

I^{131}-Labeled Triolein Capsule Meal. Shortly after this study was undertaken, radioactive triolein became commercially available in precalibrated capsules, and these capsules were used in the study of some subjects. The subject swallowed this capsule with a little barium and the remainder of the study was carried out as described.

I^{131}-Labeled Oleic Acid Study. Whenever the results of the I^{131}-labeled triolein study were abnormal, an I^{131}-labeled oleic acid study was performed after a few days, in exactly the same manner except that fasting blood and stool radioactivity was determined before the test dose of radioactive oleic acid was administered, to permit correction for residual radioactivity, if any. Pure triolein or oleic acid labeled at the unsaturated bond with radioactive iodine was obtained from Abbott Laboratories, North Chicago, Illinois, and from E. R. Squibb and Sons, New York, New York.

Chemical Determination of Fecal Fat and Nitrogen. A partial balance study, in which calculation was substituted for analysis of the fat content of weighed diets, was used as a diagnostic test for steatorrhea. After the radioactivity had been counted, the same stool specimen was then homogenized in a one gallon capacity Waring blendor and chemical fecal fat was determined in an aliquot by the method of Van de Kamer et al. [*51*]. Fecal chemical nitrogen was determined by the macrokjeldahl method.

RESULTS

Control Group. The control group consisted of twenty-four apparently healthy ambulatory volunteer subjects, mostly members of the house-staff and laboratory personnel. There were eighteen men and six women, ranging in age from twenty to forty years; the majority were in their thirties. Of these twenty-four volunteer subjects, blood radioactivity determinations were made in twenty after the oral ingestion of the triolein meal both in the emulsion form as well as in the capsule form. In the remaining four volunteer subjects, two had ingested the emulsion and two the capsule meal; only one test was performed.

Figures 1 and 2 show the mean values of blood radioactivity, and the ranges in activity after the ingestion of emulsion and capsule meals separately and combined. Table 1 shows the mean blood levels and ranges at different times

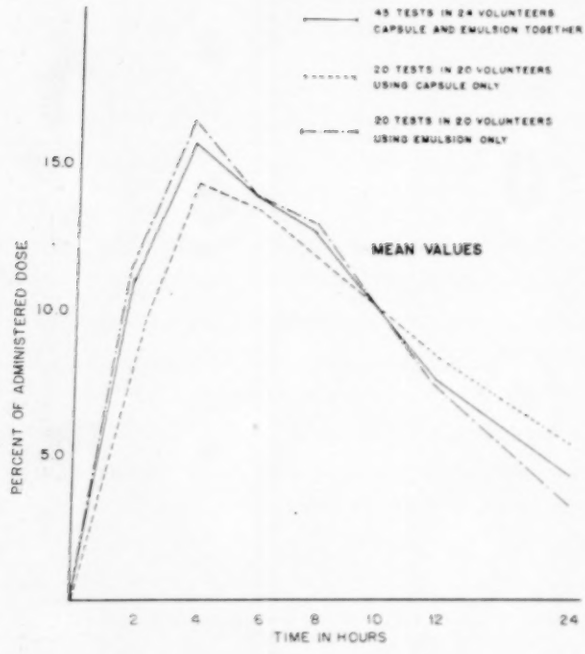


FIG. 2.

after administration of I^{131}-labeled triolein both in emulsion and capsule form. The curve following the emulsion meal was much more uniform and demonstrated a narrower spread in values whereas following the capsule meal there was a wider spread; the peak value, however, in the majority of volunteer subjects, occurred at four hours with either type of meal. There were four volunteer subjects in whom the peak did not occur until later after ingestion of the triolein capsule; in two at ten hours, in the third at fourteen hours, in the fourth at twenty-four hours. All of these four volunteer subjects showed peak blood radioactivity following the ingestion of the emulsion meal in less than six hours. Following the emulsion meal only one volunteer subject showed a peak as late as eight hours, in the remaining nineteen volunteer subjects it occurred in less than six hours.

Table II shows the peak blood radioactivity values in twenty normal volunteer subjects given both the emulsion and capsule meals of I^{131}-labeled triolein. The mean with the emulsion meal was 16.9 ± 4.1 per cent, with a range of 12 to 28 per cent and a calculated lower limit (mean ± 2 S.D.) of 8.7 per cent of the administered dose. The mean with the capsule meal was 19.6 ± 6.4 per cent, with a range of 7 to 32 per cent and a calculated lower limit (mean ± 2 S.D.) of 6.8 per cent of the administered dose. It is again noted that there was less variation in the blood peak levels following the emulsion meal. One volunteer subject (L. P.) had a peak of only 7 per cent following the capsule meal while his peak following the emulsion meal was 13 per cent. The differences between the emulsion and capsule meals were of borderline significance, the "p" value being less than 0.05.

Table II also shows the blood peak radioactivity in all twenty-four normal volunteer subjects, representing a composite total of forty-five tests with both the capsule and emulsion

TABLE I

MEAN BLOOD RADIOACTIVITY LEVELS AND RANGES AT DIFFERENT TIMES AFTER ORAL INGESTION OF I^{131} TRIOLEIN

Group*	Per cent of Administered Dose					
	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	12 Hours
A	8.9 0.3 to 27.3	14.07 0.3 to 31.5	13.2 0.4 to 25.7	11.8 1.4 to 22.8	11.6 5.4 to 22.8	5.2 1.5 to 12.0
B	11.06 3.1 to 22.4	15.98 8.6 to 28.2	13.8 10.0 to 22.0	11.7 8.8 to 20.0	... ...	3.02 0.3 to 10.3
C	10.6	15.4	13.7	12.4	11.0	4.0

NOTE: First line represents the peak, second line the range.

* A = Twenty tests in twenty normal volunteer subjects using capsule of I^{131} triolein.
B = Twenty tests in the same twenty normal volunteer subjects using emulsion of I^{131} triolein.
C = Forty-five tests in twenty-four normal volunteer subjects using both emulsion and capsule of I^{131} triolein.

TABLE II
BLOOD PEAK RADIOACTIVITY IN NORMAL VOLUNTEER SUBJECTS WITH BOTH EMULSION AND CAPSULE STUDIES

Volunteer Subject	Emulsion (%)	Capsule (%)	Combined Average (%)
B. P.	22.0	27.0	25.0
F. T.	19.0	23.0	21.0
E. T.	13.0	23.0	18.0
S. D.	16.0	13.0	16.0
J. Ca.	21.0	20.0	21.0
E. S.	19.0	25.0	22.0
E. P.	14.0	20.0	17.0
J. C.	17.0	18.0	18.0
A. P.	13.0	10.0	12.0
M. S.	17.0	21.0	19.0
B. R.	17.0	18.0	18.0
L. P.	13.0	7.0	10.0
R. H.	16.0	19.0	18.0
W. S.	15.0	21.0	18.0
M. K.	28.0	26.0	27.0
G. S.	13.0	12.0	13.0
G. R.	14.0	24.0	19.0
S. B.	21.0	32.0	27.0
P. K.	20.0	13.0	17.0
M. B.	12.0	22.0	17.0
D. W.	...	...	20.0
E. B.	...	...	32.0
C. S.	...	...	16
E. S.	...	...	16
Mean	16.9	19.6	19.0
Standard deviation	±4.1	±6.4	±5.0

meals. The mean was 19 ± 5, with a calculated lower limit of normal (mean ± 2 S.D.) of 9 per cent of the administered dose. Although this value is somewhat higher than that after the capsule meal only (6.8 per cent), it is not significantly different from that of the calculated lower limit after the emulsion meal only (8.7 per cent). As already stated, only one volunteer subject among twenty-four had a lower than 9 per cent value after the capsule meal; although this subject had a normal blood value of 13 per cent following the emulsion meal; in the subsequent discussion 9 per cent has been taken as the lower limit of normal, irrespective of the type of meal.

As previously indicated, blood volume in this study was calculated on the basis of body surface area, taking 3,000 ml. per square meter of body surface area as the normal blood volume. Baylin et al. [*6*] assumed the blood volume to be 7.2 per cent of body weight in kilograms, while Best and Taylor [*10*] suggest a factor of 7.7 per cent of the body weight in kilograms. Grossman [*26*] expressed his results in terms of the percentage of administered dose per liter of blood. To compare our results in terms of these workers' findings, we calculated the results (Table III) using their methods. It will be seen that the results expressed as 3,000 ml. per square meter of body surface area and 7.7 per cent body weight in kilograms were nearly the same. Those using 7.2 per cent of the body weight in kilograms

TABLE III
VARIATION IN BLOOD LEVELS DEPENDENT UPON CRITERIA FOR BLOOD VOLUME

Group*	2 Hours	4 Hours	6 Hours	8 Hours	10 Hours	24 Hours
A	9.5 0.0 to 32.4	14.1 0.5 to 32.4	13.7 1.5 to 23.3	11.4 2.9 to 20.4	10.9 5.4 to 22.7	3.43 0.3 to 9.8
B	9.36 0.0 to 33.5	14.1 0.5 to 33.5	13.7 1.5 to 24.0	11.4 2.9 to 21.2	10.4 5.3 to 23.2	3.5 1.0 to 9.7
C	8.7 0.0 to 30.6	13.2 0.4 to 30.6	12.8 1.4 to 22.2	10.6 2.7 to 19.3	9.8 4.9 to 21.7	3.2 1.0 to 9.0
D	1.75 0.0 to 5.9	2.55 0.07 to 5.9	2.46 0.16 to 4.35	2.06 0.48 to 3.84	2.07 1.01 to 3.78	0.67 0.15 to 1.85

NOTE: First line represents the peak, second line the range.

* A = Thirty-one tests in twenty volunteer subjects after oral I^{131} triolein (emulsion and capsule). Blood volume = 3,000 ml./M^2.
B = Same tests in same volunteer subjects. Blood volume = 7.7 per cent of body weight in kg.
C = Same tests in same volunteer subjects. Blood volume = 7.2 per cent of body weight in kg.
D = Same test values in same volunteer subjects, expressed as per cent of administered dose/liter of blood.

TABLE IV
FECAL RADIOACTIVITY IN NORMAL VOLUNTEER SUBJECTS WHO TOOK BOTH EMULSION AND CAPSULE WITH I^{131} TRIOLEIN

Volunteer Subject	Emulsion (%)	Capsule (%)
J. C.	3.0	2.0
A. P.	1.0	1.0
E. S.	1.0	2.0
R. H.	2.0	5.0
F. T.	5.0	4.0
W. S.	4.0	6.0
S. D.	5.0	4.0
L. P.	4.0	3.0
B. R.	1.0	1.0
J. C.	4.0	1.0
Mean	3.0	2.9

were, of course, somewhat lower, but not significantly different. Our results agreed fairly closely with those of Grossman et al. [*26*] when expressed as percentage of the administered dose per liter of blood. The mean peak value in our series by Grossman's method [*26*] was 3.26 ± 1.07 per cent of the administered dose per liter of blood, with a range of 1.1 to 5.9 and calculated lower limit of normal of 1.12 per cent of the administered dose per liter of blood.

Table IV summarizes the results of fecal radioactivity measurements in ten normal volunteer subjects who were given both the emulsion and the capsule meal of I^{131}-labeled triolein. The mean value was 3 per cent of the administered dose with the emulsion meal and 2.9 per cent with the capsule meal. There was no significant difference, the "p" value being less than 0.5.

Table V summarizes the results of estimation of the fecal excretion of triolein after oral ingestion both in the emulsion and capsule form in twenty volunteer subjects. The mean value was 3 ± 1.94 per cent of the administered dose, with a calculated upper limit of normal of 6.9 per cent (mean + 2 S.D.) and a range of 1 to 9 per cent. In the subsequent discussion in this paper, 7 per cent of the administered dose is taken as the upper limit of normal for fecal radioactivity. It should be noted that there was only one volunteer subject (C. S.) whose fecal radioactivity exceeded the upper limit of normal. This subject had normal fecal fat when chemically determined.

Table V also records the results of fecal fat chemical studies in thirty-one experiments on twenty normal volunteer subjects. The mean fecal fat when chemically determined was 4 ± 1.6 gm. per day, with a calculated upper limit of normal (mean + 2 S.D.) of 7.2 gm. per day and a range of 2 to 9 gm. per day. In the subsequent discussion in this paper 7 gm. per day has been taken as the upper limit of normal fecal fat when measured chemically. There was one volunteer subject (D. W.) whose fecal fat so determined exceeded the upper limit of normal. This subject had normal blood peak and fecal radioactivity values.

Table V further shows the values for the fecal wet weight, fecal dry weight and fecal fat as a percentage of the dry weight. The mean fecal wet weight in the thirty-one experiments on twenty normal volunteer subjects was 115.3 ± 41.1 gm. per day with a range of 54.5 to 202.4 gm. per day; the calculated upper limit of normal (mean + 2 S.D.) was 197.5 gm. per day. The mean fecal dry weight in the same thirty-one experiments was 34 ± 16.2 gm. per day, with a range of 14.5 to 74.7 gm. per day and a calculated upper limit of normal (mean + 2 S.D.) of 66.4 gm. per day. The mean fecal fat, chemically determined and expressed as percentage of the dry weight, was 14 ± 8.07 per cent, the calculated upper limit of normal being 30.4 per cent of the dry weight per day. The mean fecal nitrogen was 1.8 ± 0.2 gm. per day with a range of 0.8 to 2.9 gm. per day and a calculated upper limit of normal of 2.2 gm. per day.

In the subsequent discussion 7 per cent of the administered dose as the fecal radioactivity and 7 gm. per day of fecal fat, chemically estimated, has been taken as the upper limit of normal, while 9 per cent of the administered dose in the whole blood volume at any time has been taken as the lower limit of normal peak radioactivity.

Functional Disorders of the Gastrointestinal Tract. There were thirteen patients in this group, seven men and six women, ranging in age from fourteen to seventy years. The duration of disease varied from two months to fifteen years. All the patients had diarrhea, although this was not the presenting symptom in two. In some the diarrhea alternated with constipation. Abdominal pain, mostly crampy in nature, was present in twelve of these thirteen patients. All had some type of anxiety.

The hemoglobin was less than 11 gm. per 100 ml. in only one patient. The serum alkaline

TABLE V

FECAL AND BLOOD VALUES IN NORMAL VOLUNTEER SUBJECTS

Volunteer Subject	Fecal Values					I^{131} Triolein	
			Chemical				
	Wet Weight (gm./day)	Dry Weight (gm./day)	Fat (% of dry weight)	Fat (gm./day)	Nitrogen (gm./day)	Blood Peak (% administered dose)	Fecal (% administered dose)
B. P.	194.0	28.3	26.4	7.0	1.8	25.0	3.0
F. T.	179.5	25.9	13.8	4.0	2.0	21.0	5.0
E. T.	81.9	22.9	28.9	7.0	1.4	18.0	3.0
S. D.	101.2	31.0	9.0	3.0	2.1	16.0	5.0
P. K.	86.2	14.5	15.9	2.0	0.9	17.0	3.0
D. W.	168.8	34.0	26.3	9.0	1.9	20.0	2.0
J. C.	154.7	22.6	14.3	5.0	2.0	21.0	3.0
E. B.	54.5	19.5	21.2	4.0	1.2	32.0	1.0
E. S.	90.5	22.6	18.2	4.0	0.9	22.0	2.0
J. C.	112.9	54.5	6.6	4.0	1.8	18.0	3.0
A. P.	74.8	30.8	22.2	4.0	1.4	12.0	1.0
R. H.	131.2	31.4	10.1	3.0	2.3	18.0	4.0
W. S.	108.8	52.1	6.1	3.0	2.8	18.0	5.0
L. P.	115.8	27.3	15.8	5.0	1.4	10.0	4.0
B. R.	88.1	20.0	19.4	4.0	2.5	18.0	1.0
C. S.	199.1	77.9	6.6	5.0	2.5	16.0	9.0
E. P.	101.9	34.7	15.1	5.0	1.0	17.0	3.0
E. S.	134.0	62.1	4.1	3.0	1.8	16.0	2.0
M. S.	80.5	30.8	7.9	2.0	1.2	19.0	2.0
D. B.	67.0	29.3	11.2	4.0		27.0	2.0
M. K.						27.0	
G. S.						13.0	
G. R.						19.0	
M. B.						17.0	
Mean	115.3	34.0	13.3	4.0	1.8	19.0	3.0
Standard deviation	±41.1	±16.2	±8.07	±1.6	±0.2	±5.0	1.94
Normal	<197.5	<66.4	<30.4	<7.2	<2.2	>9.0	<6.9

phosphatase was normal in the seven cases in which it was determined. Bromosulphalein retention (eleven patients) was equivocally increased in six. The serum cholesterol, amylase and lipase were normal in the patients in whom measured. A glucose tolerance test was carried out in nine patients, results were normal in eight and of the diabetic type in one. Nine patients showed neither hypoproteinemia nor hypoalbuminemia. Of those patients who had barium progress meal studies six showed hypermotility while motility was normal in the remaining four.

Table VI shows the fecal values as well as the blood peak and fecal radioactivity values in these cases. The mean fecal wet weight was 218.3 ± 79.9 gm. per day, with a range of 128.8 to 401.2 gm. per day; this was significantly different from the normal subjects, the "p" value being less than 0.001. The mean fecal dry weight was 47.5 ± 25.4 gm. per day, with a range of 15.3 to 106.9 gm. per day, and was not significantly different from the normal values, the "p" value being less than 0.2. The mean fecal fat determined chemically and expressed as percentage of the dry weight, was 8.1 ± 8.6 per cent of dry weight, with a range of 2.3 to 34 per cent of dry weight. This value is not significantly different from the normal, the "p" value being

TABLE VI
FECAL AND BLOOD VALUES IN FUNCTIONAL DISORDERS

Patient	Fecal Values					I^{131} Triolein (% administered dose)	
	Wet Weight (gm./day)	Dry Weight (gm./day)	Chemical			Fecal Radioactivity (%)	Blood Peak (%)
			Fat (% of dry weight)	Fat (gm./day)	Nitrogen (gm./day)		
R. R.	149.8	22.8	10.0	2.3	1.5	2.0	13.0
L. H.	144.7	19.8	6.6	1.3	0.7	1.0	21.0
S. H.	327.6	53.5	10.8	5.8	1.2	1.0	24.0
H. S.	401.2	106.9	3.2	3.4	1.9	1.0	12.0
I. S.	283.3	38.0	13.2	5.0	2.0	1.0	14.0
V. F.	230.0	45.9	5.0	2.3	1.4	1.0	21.0
D. H.	224.6	42.5	3.1	1.3	1.8	1.0	7.0
W. A.	231.8	82.2	2.2	1.8	1.3	2.0	15.0
L. K.	208.1	15.3	34.0	5.2	2.0	3.0	17.0
J. E.	196.3	48.4	3.9	1.9	1.5	5.0	11.0
B. D.	159.9	64.1	2.3	1.5	1.3	5.0	31.0
I. A.	151.8	44.2	8.4	3.7	1.4	1.0	14.0
J. U.	128.8	34.4	3.2	1.1	1.0	1.0	23.0
Mean	218.3	47.54	8.1	2.82	1.46	1.92	17.1
Standard deviation	±79.9	±25.4	±8.6	±1.64	±0.12	±1.5	±6.5

less than 0.1. The mean fecal fat, as determined chemically and expressed in absolute weight, was 2.82 ± 1.64 gm. per day with a range of 1 to 5. It should be noted that this value is well within our normal range and of borderline significance in that it is lower than our normal mean, the "p" value being less than 0.05. The mean fecal nitrogen was 1.46 ± 0.12 gm. per day, with a range of 0.7 to 2 gm. per day. This value also is within our normal limits.

The mean blood peak radioactivity after an I^{131}-labeled triolein meal was 17.1 ± 6.5 per cent of the administered dose, with a range of 7 to 31 per cent of the administered dose. This value is well within our normal range and there is no statistical difference in the means the "p" value being less than 0.2. The mean fecal radioactivity after the I^{131}-labeled triolein meal was 1.92 ± 1.5 per cent of the administered dose, with a range of 1 to 5 per cent of the administered dose. It should be noted that this value also is well within our normal range, although it is of borderline significance in that it is lower than our normal mean, the "p" value being less than 0.05.

There was thus no significant difference between the various fecal values, and blood peak and fecal radioactivity values of normal volunteer subjects and patients with functional disorders except in respect to the wet weight of feces. The fecal wet weight was significantly elevated in patients with functional disorders, due to an increased amount of water since the dry weight, fecal fat and nitrogen values were comparable in both groups.

COMMENTS

In the group of normal persons the mean fecal wet weight was 115.3 ± 41.1 gm. per day, the calculated upper limit of normal (mean + S.D.) being 197.5 gm. per day. These values are in agreement with previous reports. The mean fecal dry weight in the same studies was 34.0 ± 16.2 gm. per day, the calculated upper limit of normal being 66.4 gm. per day. This value is somewhat higher than the values reported by Wollaeger et al. [*59,60*] and may be due to the fact that our volunteer subjects were allowed a free intake of salads without rich dressings.

The mean fecal fat, as determined chemically,

TABLE VII

RESULTS OF ANALYSIS OF FAT IN FECES FROM NORMAL SUBJECTS

Investigator	No. of Subjects	Duration of Observation (days)	Daily Fat Intake (gm.)	Daily Fat Excretion (gm.)
Deucher, 1898	1	3	203	6.3
Gross, 1912	1	2	168	4.2
Garrod, Hurtley, 1912	1	3	177	1.4
Schmidt, 1915	3	3	111	6.1
Spriggs, Leigh, 1915	1	3	136	5.4
Pratt, 1934	7	3	132	3.3 to 13.2
Wang, Hogden, Genther, 1939	6	6	72–83	1.8 to 3.4
Macy, 1942	515	5	79.3 ± 16.58	3.47 ± 0.44
Rekers, Abels, Rhoads, 1943	2	3–4	120 to 130	3.1 to 6.3
Rekers, Abels, Rhoads, 1943	2	3	200 to 210	6 to 8 ?
Cooke et al., 1946	50	2–4	50	2.5 ± 2.0
Wollaeger et al., 1947	11	5–6	102	4.1 ± 1.5 Range 1.8 to 6.7
Annegers, 1948	40	5	93 to 168	3.91 ± 1.56
	40	30 days	"	3.91 ± 1.01
Fouruman, 1948	...	...	70	2.88 Upper limit 5.7
Cooke, 1953	48	Daily	50	2.7 ± 0.95
	5	"	50 to 75	3.33 ± 1.5
Crowe, 1956	12	3–4	68	2.6 ± 1.77 Range 0.9 to 6.2
	18	3–4	Less than 150	2.3 ± 0.8 Range 0.9 to 4.2
Gardner, 1956	6	3–4	70	3.5 Range 2.7 to 5.3

was 4.0 ± 1.6 gm. per day, with a calculated upper limit of normal of 7.2 gm. per day. This value is in agreement with published reports. (Table VII.) The mean fecal (chemical) fat as a percentage of the dry weight was 14 ± 8.07 per cent, the calculated upper limit of normal being 30.4 per cent of the dry weight per day. The mean fecal nitrogen was 1.8 ± 0.2 gm. per day, with a calculated upper limit of normal (mean + 2 S.D.) of 2.2 gm. per day. The mean values for these three parameters are practically the same as reported by Wollaeger [*59*], as are the cited ranges and upper limits of normal for fecal fat and nitrogen in grams per day. Only the range and upper limit of normal for the fecal dry weight in our series of normal subjects is higher than that reported by Wollaeger [*59*] and this may be due, as already mentioned, to the unlimited intake of salads.

The mean fecal radioactivity was 3 ± 1.94 per cent of the administered dose, the calculated upper limit of normal (mean + 2 S.D.) being 6.9 per cent of the administered dose, with a range of 1 to 9 per cent of the administered dose. Saunders and his associates [*38,40,41*] reported the mean fecal radioactivity in their normal subjects to be 0.6 per cent, with a calculated upper limit of normal of 2 per cent but a range of 0 to 6 per cent. They, however, collected stool specimens for only forty-eight hours. McKenna et al. [*35*] have shown that fecal radioactivity values increased to a certain extent as the period of fecal collection was increased up to seventy-two hours. In their series of seven control patients a range of 1.1 to 4 per cent recovery of the ingested dose was obtained in seventy-two–hour stool specimens. Five of their control subjects had forty-eight–hour stool specimens which showed a range of 0.7 to 1.5 per cent recovery of the ingested dose. In two of their control subjects only twenty-four–hour specimens were obtained and these showed 0.3 to 0.7 per cent recovery. Beres et al. [*7*] collected stool specimens for seventy-two to ninety-six hours in five normal patients, with a fecal recovery of 1 per cent or less. Spencer and Mitchell [*47*] determined only fecal radioactivity after a I^{131}-labeled triolein meal in ten patients without chronic pancreatic

disease and in eleven other patients with chronic pancreatitis and other gastrointestinal diseases. The average fecal recovery in the ten patients without pancreatic disease was 1.5 per cent, with a range of 0.1 to 2.4 per cent. They gave these patients charcoal with the triolein and collected the stool specimens until traces of charcoal no longer appeared, but they do not specify the duration of the stool collection. Grossman and Jordan [*26*] conducted studies on twenty-six subjects who did not have steatorrhea on either clinical grounds or on the basis of chemical determination of fecal lipid excretion. They found the mean fecal recovery in these patients to be 2.7 ± 1.2 per cent, with a range of 0.7 to 6.1 and a calculated upper limit of normal 5.1 per cent of the administered dose in seventy-two hours.

It should be pointed out here that the control subjects used by these various groups, with the exception of Ruffin, were patients whereas in our study all the control subjects were normal volunteer subjects, mostly members of the house staff and laboratory personnel. In our procedure stool specimens were collected until there was no significant residual radioactivity while most of the authors cited collected the stools for a specified period. The mean fecal radioactivity values in the control groups of our series, of the series reported by McKenna et al. [*35*] and by Grossman et al. [*26*] are nearly the same, while the calculated upper limit of normal as well as the range is somewhat higher in our series than that reported by Grossman et al. This may be explained by the fact that the collection period in our series was longer.

Our studies also confirm the finding of Isley et al. [*29*] that there was no significant difference in the fecal radioactivity recovery using either capsule or emulsion meal.

Total blood peak radioactivity after I^{131}-labeled fat meals was determined in forty-five experiments on twenty-four volunteer subjects. (Table II.) The mean was 19 ± 5 per cent, the calculated lower limit of normal being 9 per cent of the administered dose. The mean blood peak with the emulsion meal was 16.9 ± 4.1 per cent of the administered dose, with a range of 12 to 28 per cent and a calculated lower limit (mean − 2 S.D.) of 8.7 per cent of the administered dose. With the capsule, the mean was 19.6 ± 6.4 per cent of the administered dose, with a range of 7 to 32 per cent of the administered dose and a calculated lower limit (mean − 2 S.D.) of 6.8 per cent of the administered dose. It is to be noted again that there was shorter range in the blood peak values with the emulsion meal than that with the capsule meal. The differences between the emulsion and capsule meals were significant, the "p" value being less than 0.05.

There are several ways in which blood radioactivity values have been described. In the original method of Stanley and Thannhauser [*52*] the values were expressed as a percentage of the administered dose per 100 ml. of serum while Ruffin [*38*], who has probably used this test on a wider scale than anyone else, expressed the results as a percentage of the administered dose in the whole blood volume at any particular hour. McKenna et al. [*35*], Beres et al. [*7*], Duffy and Turner [*18*] and Reemtsma et al. [*37*] measured the lipid bound I^{131} rather than the whole blood. Berkowitz and Sklaroff [*9*] used Ruffin's technic but emphasized the importance of the peak value irrespective of the time of its occurrence. Grossman and Jordan [*26*] have expressed the results as a percentage of the administered dose per liter of whole blood. They have also pointed out that their statistically determined lower limit of normal was distinctly lower than any of the observed values and, hence for blood values they adopted an empiric lower limit of normal, namely, the next to the lowest observed value in the control group. Kaplan et al. [*31*] express their results in the same manner as Grossman and Jordan [*26*].

All authors used subjects who had been fasting overnight. In Stanley and Thannhauser's original method [*52*] radioactive I^{131}-labeled olive oil was administered with bread. Shingleton [*6,3,8, 40,41,43–45*] used peanut oil emulsions, also commercial gelatin capsules with triolein. Beres [*7*] prepared an emulsion of radioactive triolein, olive oil, milk and ginger ale while Kaplan et al. [*31*] used triolein homogenized with milk. McKenna et al. [*35*] gave triolein mixed with olive oil with, or shortly after, breakfast. Spencer et al. [*47*] and Berkowitz et al. [*9*] prepared emulsions according to Shingleton's technic. Grossman and Jordan [*26*] gave triolein in gelatin capsules.

We have prepared the triolein meal according to the Ruffin method [*6,38–40,43–45*] and expressed the results of blood radioactivity as the percentage of the administered dose present in the whole blood, assuming 3,000 ml. per square meter of body surface area as the normal blood volume.

The various authors have also used different time schedules in the withdrawal of blood after the ingestion of the triolein meal. Stanley and Thannhausser [*52*] withdrew blood every hour for twelve hours, with an additional specimen at twenty-four hours. Ruffin [*38–40*] measured hourly blood samples for six hours and originally expressed the results in terms of the sum of total radioactivity in the whole blood at four, five and six hours. If this total was 40 per cent or more of the administered dose, fat absorption was considered normal. More recently these authors were of the opinion that, if the mean of the four-, five- and six-hour blood samples was more than 8 per cent of the administered dose, the value was within normal limits. If the average of these three samples was less than 5 per cent it was assumed that marked impairment of absorption had taken place; averages between 5 and 8 per cent were presumed to represent moderately impaired absorption. These levels were assumed empirically and were not statistical levels. Beres et al. [*7*] withdrew blood at two, four, six and eight hours only and determined only the lipid-bound activity. In expressing their results they used only 1 S.D. and compared the mean curves instead of the peaks. McKenna [*35*] withdrew blood at one, two, three, four, six and sometimes at nine, twelve, twenty-four and forty-eight hours. Radioactivity was counted on 2 cc. of serum and the results expressed as microcuries per 100 milliliters of serum.

In this series only one volunteer subject had a peak blood radioactivity value which was lower than the calculated lower limit of normal. There were four others in whom the blood peak did not occur before ten hours and would have been missed had not blood specimens been drawn until a peak was reached. This occurred more frequently after the capsule type of meal and suggests that blood specimens should be drawn until a peak value is reached and not for an arbitrary limit of eight or ten hours, as some reports indicate.

Although there was no significant difference in the mean fecal radioactivity values after either the capsule or emulsion type of triolein meal, the blood radioactivity curve after the emulsion meal was much more uniform and was less likely to give false low values. (Fig. 1.) In this respect our results in the control group definitely are somewhat divergent from those of Isley et al. [*29*]. If the I^{131}-labeled triolein meal is to be used to detect malabsorption, and if only blood radioactivity values are to be determined, it is better to use the emulsion meal than the capsule test. If fecal radioactivity also is determined, this difference would take on less clinical significance.

There were thirteen patients in the group of functional disorders (Table VI) and all had fecal fat (chemically determined) and nitrogen values within the range of normal, in agreement with published data. All thirteen patients had normal fecal radioactivity values after oral ingestion of the I^{131}-labeled triolein meal. One patient had an abnormally low blood peak radioactivity after the I^{131}-labeled triolein emulsion but peak radioactivity occurred twenty-four hours after the capsule.

When, in a given study, the fecal fat as determined chemically was abnormal and the fecal radioactivity and/or blood peak radioactivity was within the normal range, this was defined as a false negative. On the other hand, if the chemical fat was normal and the fecal and/or blood peak radioactivity was abnormal, this was called a false positive for steatorrhea. In the group of patients with functional disorders there were no false negative results by either the blood peak or fecal radioactivity tests, and only one false positive result by the blood peak radioactivity test. There were no false positive results by the fecal radioactivity study.

Six of our patients with functional disorders demonstrated hypermotility on the barium progress meal examination. None of these patients showed evidence of steatorrhea either by the fecal balance study or by the fecal radioactivity test. One of this group previously mentioned had a decreased blood peak radioactivity while all of the others had normal blood peaks. We have not encountered any patient with simple hypermotility of the bowel who had steatorrhea.

Baylin et al. [*6*] previously presented data on forty-four patients with functional diarrhea. The mean fecal excretion in forty-eight hours in these patients was 1.2 per cent, with a range of 0 to 2.8. These values were within the limits of what they considered to be normal. The blood absorptive pattern also was normal in all forty-four patients. Subsequently, these authors [*40*] presented additional data on 113 patients with functional diarrhea, all of whom had a normal absorptive pattern.

It should be pointed out that Ruffin et al., who have studied triolein absorptive patterns in

these groups, have classified functional diarrhea as a separate entity while others have included this type of patient in their group of normal subjects.

Klotz et al. [*32*] demonstrated alteration of radioactive fat absorption by increasing intestinal motility with castor oil in otherwise normal subjects. Patterns of excretion were studied for various time intervals of purgation after tracers were administered. The results showed that excretion of fat was well above the limits of normal. It should be realized that there is a basic difference in the hypermotility of functional diarrhea and the hypermotility caused by the use of castor oil, which is an irritant cathartic.

CONCLUSIONS AND SUMMARY

Fecal balance studies using standard chemical technics, and blood peak and fecal radioactivity determinations were carried out after the administration of radioactive iodine-labeled triolein in twenty-four normal volunteer subjects and thirteen patients with functional disorders of the gastrointestinal tract. The I^{131}-labeled triolein meal was administered in capsule as well as emulsion form. Fecal wet weight, dry weight, fat (chemical) and nitrogen were determined, as was the fecal radioactivity. These specimens were collected until there was no significant residual radioactivity; carmine was used as a marker for the balance study. Blood radioactivity was determined in serial samples until a peak value of uptake was reached.

Twenty volunteer subjects were given both the emulsion and capsule type of triolein meal. It was found that the blood absorptive curve after the emulsion meal was much more uniform, with a narrower range in values, whereas with the capsule meal there was greater variation, although the peak value in the majority of volunteer subjects occurred four hours after ingestion of either type of meal. Since the blood peak is the most important value in the absorptive pattern, only these values were considered.

The mean blood peak radioactivity in forty-five experiments on twenty-four normal volunteer subjects, using both capsule and emulsion type of triolein meal, was 19 ± 5 per cent of administered dose, the calculated lower limit (mean −2 S.D.) being 9 per cent of the administered dose.

The mean fecal excretion of triolein after the oral ingestion of triolein both in emulsion and capsule form in thirty-one experiments on twenty normal volunteer subjects was 3 ± 1.94 per cent of the administered dose, with a calculated upper limit of normal (mean + 2 S.D.) of 6.9 per cent of the administered dose and a range of 1 to 9 per cent. It was found that there was no significant difference in fecal radioactivity values after either capsule or emulsion type of triolein meal. As a result of these studies we believe that when malabsorption is measured by blood radioactivity, the emulsion meal is preferable to the capsule technic. If fecal radioactivity also is assayed, there is less clinical significance in the differences between these two types of meals provided a peak blood value is demonstrated.

The mean fecal fat (chemically determined), expressed as grams per day, was 4 ± 1.6 gm. per day, ranging from 2 to 9 gm. per day with a calculated upper limit of normal (mean + 2 S.D.) of 7.2 gm. per day.

There were no significant differences in the various fecal studies and the blood peak and fecal radioactivity values between the normal volunteer subjects and the patients with functional disorders, except in the values for fecal wet weight. Wet weight was significantly increased in patients with functional disorders, probably due to an increased amount of water, since the dry weight, (chemical) fat and nitrogen values were nearly the same in both groups.

Six patients with small bowel hypermotility did not have any defect in absorption of fat as determined by the fecal balance study or the radioactive triolein tests.

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Correlation of Radioactive and Chemical Fecal Fat Determinations in Various Malabsorption Syndromes*

II. Results in Idiopathic Steatorrhea and Diseases of the Pancreas

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The diagnosis of idiopathic steatorrhea is usually made by the demonstration of malabsorption of various substances and by histologically demonstrated atrophic changes in the small bowel mucosa in the absence of exocrine pancreatic deficiency. The diagnosis of chronic relapsing pancreatitis is seldom difficult when the three diagnostic sequelae, namely, diabetes, calcification of the pancreas and gross steatorrhea are demonstrable. However, in the interval between acute episodes, when the values for diagnostic enzymes in the serum are not elevated and when the characteristic sequelae have not yet developed, a presumptive diagnosis may be made by certain clinical features of the acute episodes and by exclusion of other diseases of the upper part of the abdomen. The diagnosis can be proved only by the demonstration of a deficiency of external pancreatic secretion.

Several methods to test exocrine pancreatic function have been used [*2,13–15,29–31,33,45*]. Dornberger et al. [*13*] claimed that, if pancreatic deficiency is responsible for excessive loss of fat, the extent of pancreatic damage is roughly proportional to the output of fat in the stools. Kalser et al. [*31*] found that, when the bicarbonate content of the duodenal juice after secretin stimulation was less than 60 mEq. per L., steatorrhea invariably was present. These latter workers expressed the view that fecal balance studies were too expensive and laborious, and moreover had a limited usefulness in the diagnosis of chronic pancreatitis, but that the secretin test, with determination of the volume and bicarbonate content of pancreatic excretion, was probably the most specific method in diagnosis [*13–15,30–33*].

Baylin et al. [*4,36–42*] have described the use of I^{131}-labeled fat as a test material for study of the fat absorption in both animals and man. These investigators found that in patients with disease of the small bowel, regardless of cause, blood radioactivity levels were not as high as in normal subjects and the radioactive content of the stool was higher than in normal subjects after ingestion of a labeled neutral fat (triolein) or fatty acid (oleic acid). They also pointed out that the evidence in patients with disease of the pancreas pointed to faulty digestion rather than to an intrinsic error of absorption. These investigators concluded that administration of radioactive fat provided a simple, accurate and reliable test of fat absorption.

Ruffin et al. [*38*] recorded blood radioactivity values after ingestion of a triolein meal in patients with carcinoma of the pancreas, chronic pancreatitis and acute pancreatitis. They concluded that 86 per cent of patients with carcinoma of the pancreas and nearly 50 per cent of patients with chronic pancreatitis had moderate or marked impairment of triolein absorption while the test result was likely to be normal or show only a

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moderate impairment in acute pancreatitis. In an earlier report Shingleton and co-workers had reported [*41*] fecal values in ten patients with carcinoma of the pancreas and eight patients with chronic pancreatitis. According to their criteria, fecal values were abnormal in all but one patient in each group. Beres et al. [*6*] had also found that, although there was good correlation between the I^{131} triolein test and steatorrhea in pancreatic disease, this test failed to detect mild impairment of pancreatic function because of the functional reserve of the pancreas.

Berkowitz et al. [*7*] found significantly lower than normal blood isotope levels in ten patients with chronic pancreatitis; while in a group of ten patients with a history of a previous episode of acute pancreatitis who did not have steatorrhea, the blood values were within normal limits. These authors do not mention the fecal recovery rate.

Reemtsma et al. [*35*] reported on the comparative absorption of labeled fat and fatty acid in pancreatic disease and concluded that patients with proved pancreatic deficiency showed a marked impairment of neutral fat absorption but normal fatty acid absorption. Patients with malabsorption due to causes other than pancreatic deficiency exhibited marked impairment of both neutral fat and fatty acid absorption. The same authors later [*40*] reported on the sweat chlorides and intestinal fat absorption in chronic obstructive pulmonary emphysema and fibrocystic disease of the pancreas. Blood isotope levels at two, four, six and twenty-four hours after ingestion of triolein meal were recorded in ten normal patients, ten patients with emphysema and two patients with fibrocystic disease of the pancreas. All these patients also had ingested an I^{131} oleic acid meal. Six of the ten patients with emphysema demonstrated impaired absorption of neutral fat; in two, altered fatty acid absorption was observed. Four of the six patients with emphysema and impaired absorption of neutral fat also had positive reactions to sweat tests, but all had normal enzymes in the duodenal drainage. Both subjects with fibrocystic disease demonstrated impaired absorption of neutral fat, in one the absorption of fatty acid was normal. Duodenal drainage in both these patients showed almost complete absence of trypsin. These authors did not collect stools for fecal recovery; they do not mention gastric emptying. Three of their six patients who had abnormal absorption of neutral fat had peak blood radioactivity at twenty-four hours, and blood isotope activity in one other patient was still on the ascending limb of the absorption curve at six hours; a peak value in this particular patient could have been reached anytime between six and twenty-four hours. The remaining two patients had peak blood radioactivity at two hours. Of the two patients who had abnormal absorption of fatty acid, one had a peak value at twenty-four hours and in the other the value was still rising at six hours (after which no blood specimens were withdrawn).

Spencer and Mitchell [*43*] measured only fecal recovery after ingestion of the triolein meal and found an increased excretion in five patients with chronic pancreatitis but a normal value in one patient who had had only one episode of acute pancreatitis. Kaplan et al. [*32*] also recorded abnormal values after ingestion of the triolein meal in three patients with chronic pancreatitis. Absorption of oleic acid was normal in these three patients. Only blood radioactivity was determined.

Turner [*46*] studied triolein absorption in six patients with calcific pancreatitis and six patients with chronic recurrent pancreatitis. Blood isotope values following the ingestion of a triolein meal were reduced in all. Four of these had an oleic acid meal, which yielded normal blood radioactivity values. The effect of a preparation of hog pancreas (Viokase,® Viobin Corporation) on the I^{131} triolein tolerance curves of six patients suffering from calcific pancreatitis was studied. When Viokase was added to the triolein emulsion fed to the patients the tolerance curves of five of the six patients were greatly increased.

The purpose of this report is to provide further data on the constituents of the feces in malabsorption syndromes. Specifically, the daily excretion of total solids, fat and nitrogen has been determined (fat-nitrogen balance study). The values for fecal fat, as determined chemically, are compared with the blood peak and fecal radioactivity values after ingestion of an I^{131}-labeled triolein meal. Ten patients with idiopathic steatorrhea and twenty patients with diseases of the pancreas form the chief subjects of this report.

METHOD

All subjects were evaluated clinically. Laboratory studies included the appropriate radiologic, hematologic and biochemical examinations, according to

need. The method of preparing the radioactive fat meal and the methods employed in the balance studies are described in detail elsewhere [*31*].

RESULTS

Idiopathic Steatorrhea. There were ten patients in this group, seven females and three males. The duration of the disease varied from one month to thirty-two years. All patients had diarrhea, bloating, weight loss and asthenia; 50 per cent also had hematuria. Two patients exhibited marked tetany; it was mild in three others. Anemia, with hemoglobin values of less than 11 gm. per 100 ml., was present in 80 per cent of the patients. Hypoprothrombinemia, with values less than 60 per cent of normal, was present in 80 per cent. Serum total protein concentrations of less than 6 gm. per 100 ml. were noted in 80 per cent while hypoalbuminemia of less than 3 gm. per 100 ml. was recorded in 70 per cent of the patients. Serum calcium was less than 9 mg. per 100 ml. in seven patients, or 70 per cent. Abnormal bromsulfalein retention was found in three of seven patients, later returning to normal in two of these. In the third patient hepatitis developed, presumably from blood transfusions.

In addition to the well known x-ray signs of dilatation, segmentation, fragmentation and moulage, there was definite coarsening of the duodenal mucosa in 80 per cent of the patients. The duodenal bulb was dilated in three, measuring more than 5 cm. in width and 5 cm. in length. These duodenal changes disappeared with clinical remission.

A radioactive vitamin B_{12} excretion (Schilling) test was performed in seven untreated patients; results were abnormal in five. The two with a normal reaction to the Schilling test were in clinical remission although steatorrhea was still present. The test was repeated in three patients who had been on a gluten-free diet from one month to one year; it returned to normal levels in two patients but in the third (M. G.) the reaction to the Schilling test remained abnormal although the steatorrhea had disappeared completely. (However, results of a third test, two and a half years after she had been on a gluten-free diet, were normal). Whole blood and platelet serotonin and urinary 5HIAA levels were elevated in all untreated patients; these values returned to normal after treatment. Six subjects had a peroral small bowel biopsy. Histologic abnormality was noted in all untreated patients with sprue.

Results of the secretin test were entirely within normal limits in respect to volume, bicarbonate content and serum enzymes in four untreated patients with sprue. In one patient (S. S.) there was a slight decrease in the bicarbonate content but otherwise the reaction was normal. There was a high fasting serum amylase and lipase concentration in another patient (M. W.) which returned to normal levels after the injection of secretin; this patient had a normal volume and bicarbonate concentration in the duodenal aspirate.

The mean fecal wet weight in these ten patients was 515 $\pm$ 84.1 gm. per day, with a range of 201 to 980.7 gm. per day. The mean fecal dry weight was 107.6 $\pm$ 42 gm. per day, with a range of 36.3 to 352.8 gm. per day. The mean fecal fat, chemically determined, was 26.7 $\pm$ 13.4 gm. per day, with a range of 15 to 59 gm. per day; expressed as the percentage of dry fecal weight, the mean fecal fat was 31.8 $\pm$ 14.1, with a range of 6.7 to 62.2 per cent of dry matter. All of these values are abnormal, the "p" value for each being less than 0.001.

Fecal excretion of nitrogen was increased to more than the calculated upper limit of normal in eight of ten untreated patients with sprue. The mean fecal nitrogen was 3.3 $\pm$ 0.45 gm. per day, with a range of 1.2 to 5.8 gm. per day, significantly abnormal. The fecal nitrogen values were not excessively high in any case but four of ten patients showed slight abnormality.

All ten patients had I^{131} triolein tests. Blood peak and fecal radioactivity in eight untreated patients with sprue was abnormal, two patients (V. T. and R. G.) had normal blood peak values. One patient (V. T.) also had normal fecal recovery of triolein on two occasions whereas the first time she was tested she had a blood peak radioactivity of 8 per cent of the administered dose, which is lower than the calculated lower limit of normal. Another patient (R. G.) had an abnormal fecal radioactivity value. Both of these patients were in clinical remission at the time of the study although their fecal fat was still abnormal.

Table 1 shows the blood peak radioactivity, fecal radioactivity and fecal fat, chemically determined, in eleven tests on these ten patients suffering from idiopathic steatorrhea. The mean blood peak radioactivity after the I^{131}-labeled triolein meal was 6.8 $\pm$ 5 per cent of the admin-

TABLE I
I^{131} TRIOLEIN AND FECAL CHEMICAL BALANCE STUDIES IN PATIENTS WITH IDIOPATHIC STEATORRHEA

Patient	Blood Peak Radioactivity (% of dose)	Fecal Radioactivity (% of dose)	Chemical Fecal Fat (gm./day)
M. G.	6.0	9.0	23.0
V. T.	8.0	1.0	42.0
	17.0	6.0	16.0
F. T.	2.0	51.0	24.0
S. S.	6.0	36.0	29.0
I. S.	7.0	26.0	15.0
C. C.	8.0	23.0	29.0
M. W.	2.0	63.0	24.0
R. B.	4.0	55.0	15.0
J. H.	1.0	63.0	59.0
R. G.	14.0	45.0	18.0
Mean	6.8	34.4	26.7
S.D.	±5.0	±22.8	±13.4
t	6.7	6.14	7.47
P	<0.001	<0.001	<0.001

istered dose, with a range of 1 to 17 per cent of the administered dose. The mean fecal radioactivity was 34.4 ± 22.8 per cent of the administered dose, with a range of 1 to 63 per cent of the administered dose. Both of these mean values are quite significantly abnormal, the "p" value for both being less than 0.001.

Four of these ten patients with idiopathic steatorrhea were studied again after they had been on a gluten-free diet for varying periods ranging from one week to one year. Although there was definite improvement, the values were still lower than normal. In two patients (M. G. and I. S.) the blood peak radioactivity, fecal radioactivity, fecal (chemical) fat and nitrogen values returned to normal levels with a strict gluten-free regimen. One patient (I. S.) was inadvertently given two slices of bread on the first day when his triolein test was being repeated and, despite this small amount of gluten, his fecal fat, chemically determined, was abnormal while his triolein values both in blood and feces were normal. After a strict gluten-free regimen for only one week, the triolein and chemical balance study was repeated. The blood radioactivity returned to normal while fecal radioactivity, fecal (chemical) fat and nitrogen values remained in the abnormal range, although definitely improved. Another patient (J. H.) had been on a gluten-free diet for only one month when her fecal fat, as measured chemically, decreased from 59 to 11 gm. per day. This patient was in clinical remission at this time. Although the blood radioactivity in this patient did not change significantly, there was a definite decrease in the fecal radioactivity, from 64 to 39 per cent of the administered dose. There was also a concomitant decrease in the fecal nitrogen excretion.

The fecal wet weight, dry weight and fecal fat (expressed as percentage of dry weight) were decreased in all patients. The mean wet weight of the stools in this treated group of patients with idiopathic steatorrhea was 184 ± 28 gm. per day, with a range of 155.5 to 214 gm. per day. The mean dry weight was 32.2 ± 1.3 gm. per day, with a range of 30.7 to 33.2 gm. per day. The mean fecal fat, chemically determined and expressed as percentage of dry fecal weight, was 20.5 ± 5.3, with a range of 14.7 to 25. It may be pointed out here that the "p" values for dry weight and for fat as percentage of dry weight were not significantly abnormal while the "p" value for wet weight was of borderline significance. The mean fecal (chemical) fat was 7.7 ± 2.6 gm. per day, with a range of 4.8 to 10.9 gm. per day. This difference was significant, the "p" value being less than 0.01. The mean fecal nitrogen was ±0.12 gm. per day, with a range of 1.4 to 2.4 gm. per day, probably not significantly different.

The mean blood peak radioactivity after an I^{131}-labeled triolein meal was 9.5 ± 5.5 per cent of the administered dose, with a range of 2 to 15 per cent of the administered dose. (Table II.) This mean value, although above the calculated lower limit of normal, is significantly abnormal, the "p" value being less than 0.001. The mean fecal radioactivity after an I^{131}-labeled triolein meal was 15 ± 17 per cent of the administered dose, with a range of 1 to 39 per cent of the administered dose. This mean value is definitely in the abnormal range, the "p" value being less than 0.01.

Eight of the ten untreated patients with sprue were given I^{131}-labeled oleic acid meals. Four of the eight patients had blood levels within the range of normal; in the remaining four it was less than the calculated lower limit of normal value. Fecal radioactivity after oral I^{131} oleic acid test was normal in two of the eight untreated patients with sprue.

Diseases of the Pancreas. There were twenty patients in this group, fourteen males and six females. Three patients (A. D., O. J. and J. P.)

TABLE II

MEAN RESULTS OF THE VARIOUS TESTS, WITH STANDARD DEVIATION AND RANGE OF VALUES

Subjects	Fecal Wet Weight (gm./day)	Fecal Dry Weight (gm./day)	Fecal (Chemical) Fat (% of dry weight)	Fecal (Chemical) Fat (gm./day)	Fecal (Chemical) Nitrogen (gm./day)	Fecal I^{131} (% administered dose)	Blood Peak I^{131} (% administered dose)
Normal volunteer	115.3 ± 41.1 54.5 to 202.4	34.0 ± 16.2 14.5 to 74.7	14.3 ± 8.0 4.1 to 37.0	4.0 ± 1.6 2.0 to 9.0	1.8 ± 0.2 0.9 to 2.8	3.0 ± 1.9 1.0 to 9.0	19.0 ± 5.0 10.0 to 32.0
Untreated idiopathic steatorrhea	515.0 ± 89.1 201.0 to 980.7	107.6 ± 42.0 36.3 to 352.8	31.8 ± 14.8 6.7 to 62.2	26.7 ± 13.4 15.0 to 59.0	3.3 ± 0.45 1.2 to 5.8	34.4 ± 22.8 1.0 to 63.0	6.8 ± 5.0 1.0 to 17.0
Treated idiopathic steatorrhea	184 ± 28.0 155.0 to 214.0	32.3 ± 1.3 30.7 to 33.2	20.5 ± 5.3 14.7 to 25.0	7.7 ± 2.6 4.8 to 10.9	2.0 ± 0.12 1.4 to 2.4	15.0 ± 17.0 1.0 to 39.0	9.5 ± 5.5 2.0 to 15.0
Acute pancreatitis	290.0 144.8 to 517.0	23.6 14.7 to 32.5	11.4 9.2 to 13.6	4.0 2.0 to 7.0	1.7 0.8 to 2.8	3.3 2.0 to 6.0	17.3 8.0 to 24.0
Chronic pancreatitis without steatorrhea	251.3 ± 94.7 103.0 to 650.0	38.6 ± 18.0 9.6 to 74.9	13.6 ± 5.8 5.3 to 20.8	4.0 ± 1.9 1.0 to 7.0	1.5 ± 0.78 0.4 to 3.3	3.8 ± 4.7 1.0 to 18.0	13.4 ± 6.3 7.0 to 28.0
Chronic pancreatitis with steatorrhea	393.4 ± 66.1 170.5 to 906.9	102.4 ± 52.8 48.8 to 207.0	23.6 ± 11.6 9.6 to 40.7	21.9 ± 15.6 8.0 to 51.0	3.7 ± 1.6 1.3 to 5.9	41.4 ± 9.6 1.0 to 95.0	7.2 ± 4.2 1.0 to 13.0

suffered from acute pancreatitis and were studied about ten to fourteen days after subsidence of the acute episode. The serum amylase was elevated in two and serum lipase in all three patients. The glucose tolerance test gave a diabetic curve in all patients whereas the reaction to the starch tolerance test (performed on two patients) was negative. All patients admitted to a heavy alcoholic intake and the acute episode followed an acute bout of "drinking." Abnormal bromsulfalein retention was noted in two of three patients in whom liver biopsy demonstrated active toxic hepatitis. The secretin test showed normal volume and bicarbonate content in two patients; one patient (J. P.) had a decrease both in volume and bicarbonate content. Serum amylase and lipase values after injection of secretin were normal in two; one patient (O. J.), who also had pyelonephritis, showed elevated serum enzymes.

The mean fecal wet weight was 290 gm. per day, with a range of 144.8 to 517.1 gm. per day. The mean fecal dry weight was 23.6 gm. per day, with a range of 14.7 to 32.5 gm. per day. Fecal fat, measured chemically, was normal in all patients but fecal nitrogen was equivocally increased in one patient (J. P.) who had decreased volume and bicarbonate content after secretin stimulation of the pancreas. The mean fecal fat, expressed as percentage of dry weight, was 11.4, with a range of 9.2 to 13.6 per cent of dry weight. The fecal radioactivity was normal in all whereas the blood peak radioactivity was decreased (to lower than the calculated lower limit of normal) in one patient (A. D.). This patient had a normal fecal fat. All three patients had I^{131} oleic acid studies in which the blood peak and fecal radioactivity studies were normal.

There were seventeen patients, eleven males and six females, suffering from either chronic or recurrent pancreatitis. One patient (L. S.), with painless chronic pancreatitis, had fecal fat (chemical) determinations on five different occasions and each time he also had an I^{131} triolein test. Two determinations were made on his first admission, two on the second admission, and one on the third admission. During the first admission the initial study was made before he was operated on for pancreatolithiasis. His second study was carried out about ten days after surgery for a single calculus in the pancreatic duct. The third examination was four months postoperatively and without any medications, the fourth study was made one week later, while he was receiving pancreatin supplement. About seven months after his second admission, or nearly one year after his first admission, he was readmitted and studied again. This time also he was receiving pancreatin supplement. He had gained about 25 pounds in weight during these seven months. Because his condition varied each time he was studied, he is taken as a

separate case each time. Another patient (T. W.) also was studied twice, about two and a half years apart. Initially he had chronic pancreatitis without obstructive jaundice; on the second occasion he had chronic pancreatitis with mild obstructive jaundice. Because of this the patient is considered a separate case each time. Based upon 7 gm. per day or less as the normal fecal fat excretion, these seventeen patients are divided into two groups, those without chemical steatorrhea (twelve patients) and those with steatorrhea (five patients).

Five patients with steatorrhea had coarsening of the second portion of the duodenum on barium meal study, five patients exhibited a "sentinel loop" on the plain film of the abdomen. A mass in the region of the pancreas was suspected in five patients. Two patients (B. P. and L. L.) had pancreatic calcification without steatorrhea and both showed evidence of pulmonary tuberculosis. One patient (B. P.) had a long history of recurrent pancreatitis with cyst, abscess and fistula formation requiring a sphincterotomy and pancreatic cyst-jejunostomy. Two patients had pulmonary emphysema. Seven of eleven patients with chronic pancreatitis admitted to moderate or heavy alcoholic intake. In only two patients (M. J. and L. L.) was there evidence of cholelithiasis but both admitted to heavy alcoholic intake and it was believed that the pancreatitis was due to chronic alcoholism rather than to gallbladder disease.

The serum amylase value was slightly elevated in five patients but only one (T. C.) showed a marked elevation. There was a borderline increase in the serum lipase in four patients; two others (M. J. and T. C.), however, showed marked elevations. Glucose tolerance tests gave a diabetic type curve in seven of ten patients. Seven of these ten patients had starch tolerance tests, results of which were positive in five. Abnormal bromsulfalein retention was present in six of nine patients.

The pancreatic fluid volume and bicarbonate content and serum amylase were each abnormal twice. The serum lipase was abnormal in four patients.

In this group the mean fecal wet weight was 251.3 ± 44.7 gm. per day, with a range of 103 to 650 gm. per day. A mean fecal dry weight of 38.6 ± 18 gm. per day, with a range of 9.6 to 74.9 gm. per day, was found. The mean fecal wet weight was higher than the calculated upper limit of normal, the "p" value being less than 0.001, while the mean fecal dry weight was in the normal range and not significantly altered, the "p" value being greater than 0.5. The mean fecal fat, expressed as percentage of dry weight, was 13.6 ± 5.8 with a range of 5.4 to 20.8 per cent of dry weight per day. This is again within our normal range and is not significantly altered, the "p" value being greater than 0.5.

The mean fecal fat, chemically estimated, was 4.08 ± 1.93 gm. per day, with a range of 1 to 7 gm. per day. This is not significantly abnormal, the "p" value being less than 0.1. Except for two patients (G. C. and T. C.), all had normal fecal nitrogen. In one patient (T. C.) there was a borderline elevation. Another patient (G. C.), who had very low bicarbonate concentration in the duodenal juice after pancreatic stimulation with secretin, had a definitely abnormal fecal nitrogen. His fecal fat was borderline normal while his triolein test result both in blood and feces was quite normal. The mean fecal nitrogen in this group was 1.46 ± 0.78 gm. per day, with a range of 0.4 to 3.3 gm. per day. This value is probably not significantly different from normal.

The blood peak radioactivity after the I^{131}-labeled triolein meal was in the normal range in all but two patients (A. K. and B. B.). The mean blood peak radioactivity was 13.4 ± 6.3 per cent of the administered dose, with a range of 7 to 28 per cent of the administered dose. This value, although above the calculated lower limit of normal, is distinctly lower than the mean value in normal subjects, the "p" value being less than 0.001. The mean fecal radioactivity in this group was 3.83 ± 4.7 per cent of the administered dose, with a range of 1 to 18 per cent. Fecal radioactivity was in the range of normal in all but one patient (L. L.). As already stated, all these patients had a normal fecal fat; the mean value was within our normal range, and not statistically significant, the "p" value being greater than 0.5.

Five of the eleven patients suffering from chronic pancreatitis without chemical steatorrhea also had I^{131} oleic acid studies. Blood peak and fecal radioactivity values were in the range of normal in all except one (M. J.), who had a decreased blood peak radioactivity. This patient had normal fecal fat and nitrogen values, and normal blood peak and fecal radioactivity values after ingestion of an I^{131}-labeled triolein meal. The mean blood peak radioactivity following I^{131} oleic acid was 14 per cent of the administered

dose, with a range of 8 to 22 per cent of the administered dose. The mean fecal radioactivity after the I^{131} oleic acid test was 1.6 per cent of the administered dose, with a range of 1 to 2 per cent of the administered dose.

Of the patients suffering from chronic pancreatitis with steatorrhea on the basis of the chemical studies, all admitted to a moderate to heavy alcoholic intake. Except for one patient (K. S.), all had pancreatic calcifications; two patients (A. R. and T. W.) also had inactive apical pulmonary tuberculosis. The serum amylase and lipase were minimally elevated in one patient (A. R.), another (T. W.) had a moderate elevation of serum lipase. One patient (L. S.) was suffering from diabetes mellitus and was taking insulin regularly. The glucose tolerance test performed in three patients gave a diabetic type curve in two, and a normal curve in only one patient. The reaction to the starch tolerance test, performed in only one subject, was positive. Results of the bromsulfalein test were within the normal range in all patients. In one patient (T. W.) mild obstructive jaundice developed later, probably due to pressure on the common bile duct by the pancreatic cyst or mass.

The secretin test was performed in all patients. The volume was decreased in three patients. All patients with steatorrhea had a decreased bicarbonate content in the duodenal juice after secretin stimulation of pancreas. Serum amylase and lipase values after secretin stimulation were normal in all but one patient (T. W.), who had a mild elevation of the serum amylase.

The mean fecal wet weight was 393.4 $\pm$ 66.1 gm. per day, with a range of 170.5 to 906.9 gm. per day. The mean fecal dry weight was 102.4 $\pm$ 52.8 gm. per day, with a range of 48.8 to 207 gm. per day. Both these values are quite abnormal, the "p" values for both being less than 0.001. The mean fecal fat, determined chemically and expressed as percentage of the dry weight, was 23.6 $\pm$ 11.6, with a range of 9.6 to 40.7. This mean value is within our normal range, with a "p" value of less than 0.2. All patients had increased fecal fat. The mean fecal fat was 21.9 $\pm$ 15.6 gm. per day, with a range of 8.0 to 51.0 gm. per day. This value is abnormal and is again quite significant, the "p" value being less than 0.001. The fecal nitrogen was increased in all except one patient (K. S.), who had minimal steatorrhea. The mean fecal nitrogen was 3.7 gm. per day, with a range of 1.3 to 5.9 gm. per day.

Blood peak radioactivity after the I^{131}-labeled triolein meal was in the range of normal in four patients and abnormal in six. The mean blood peak radioactivity was 7.2 $\pm$ 4.2 per cent of the administered dose, with a range of 1 to 13 per cent of the administered dose. This value is abnormal and significant, the "p" value being less than 0.001. The fecal recovery of I^{131} triolein after the test meal was abnormal in nine patients and normal in one. The latter (K. S.) had minimal steatorrhea. The mean fecal radioactivity value was 41.4 $\pm$ 9.6 per cent of the administered dose, with a range of 5 to 95 per cent. This value is quite abnormal and significant, the "p" value being less than 0.001.

COMMENT

The clinical findings in patients suffering from idiopathic steatorrhea were similar to those previously described [*3,10,12,17,21,25–27*].

When the values for fecal fat, fecal radioactivity and blood peak radioactivity were all normal or all abnormal, we defined this as a complete three-test agreement. On the other hand, if the fecal fat was normal and both blood peak and fecal radioactivity were abnormal, or when the fecal fat was abnormal and blood peak and fecal radioactivity was normal, this was defined as complete disagreement among the three tests. Also, in a given patient, when the fecal fat was abnormal and the fecal radioactivity and/or blood peak radioactivity was in the range of normal, the result was said to be false negative; on the other hand, if the fecal fat was normal and the fecal and/or blood peak radioactivity was abnormal, the result was called a false positive for steatorrhea. Table III shows the correlation of the fecal balance study with the I^{131} triolein test. There was complete three-test agreement in 73 per cent, complete agreement in 9 per cent. There were 17 per cent false negative tests by both blood peak and fecal radioactivity tests, and disagreement in 27 per cent by one or both tests. As discussed under results, one patient (V. T.) had two of these three tests performed one year apart. At the time of both studies this patient was in clinical remission without any specific therapy such as steroids or gluten-free diet, although her fecal fat was in the abnormal range at both times. The third patient (R. G.) in whom the diagnosis of idiopathic steatorrhea was established eighteen years before her present studies, was in clinical remission with a low fat diet and supportive treatment.

TABLE III
CORRELATION OF FECAL (CHEMICAL) BALANCE STUDY WITH THE I^{131} TRIOLEIN TESTS

Studies		Fecal (Chemical) Fat			
		Normal (7 gm./day or less)		Abnormal (more than 7 gm./day)	
		No.	%	No.	%
Combined fecal I^{131} and blood peak radioactivity in untreated idiopathic steatorrhea	Both tests normal	...	...	1	9
	One or both disagree	...	...	3	27
	Both abnormal	...	...	8	73
Combined fecal I^{131} and blood peak radioactivity in chronic pancreatitis without steatorrhea	Both tests normal	9	75	...	...
	One or both disagree	3	25	...	...
	Both abnormal	0	0	...	...
Combined fecal I^{131} and blood peak radioactivity in chronic pancreatitis with steatorrhea	Both tests normal	...	...	1	10
	One or both disagree	...	...	4	40
	Both abnormal	...	...	6	60

She had not received steroids or a gluten-free diet. Although she was in clinical remission at the time of her studies, her fecal fat was still in the abnormal range. The blood peak radioactivity after the I^{131}-labeled triolein meal was within the normal range whereas the fecal radioactivity value was abnormal.

Four patients with idiopathic steatorrhea were studied again after they had been on a gluten-free diet for a varying period of time ranging from one week to one year. Frazer [*17–19*], French et al. [*21–24*], Brown [*9*], Ruffin [*37*] and Comfort [*12*] report marked improvement in patients with steatorrhea who adhere to a gluten-free diet. Adlersberg et al. [*1,11*] and Brown et al. [*9*] found improvement in patients with steatorrhea with adrenocorticosteroid therapy. Six of ten patients with idiopathic steatorrhea had had treatment with steroids, but none of them was receiving steroids at the time of this study.

All four patients who had been on gluten-free diets showed clinical as well as laboratory improvement. The blood peak radioactivity after oral I^{131}-labeled triolein meals returned to the normal range in three of these four patients; the fourth patient showed an increased blood radioactivity value which was still in the abnormal range. Fecal radioactivity recovery was in the normal range in two of these patients (M. C. and I. S.) and improved significantly, although still in the abnormal range, in the remaining two patients (S. S. and J. H.). The fecal fat returned to the normal range in only one patient (M. G.) while in the remaining three, although it decreased considerably, it still remained in the abnormal range. These findings again suggest that the blood and fecal radioactivity levels after the I^{131}-labeled triolein meal are not as sensitive an index of steatorrhea as is the fecal fat determination by chemical means. Fecal recovery after the triolein meal seems a better index than the blood peak determination alone.

The clinical findings in patients suffering from acute or chronic pancreatitis in our series were similar to those previously recorded [*5,8,16,29,44,45,49*]. The diagnosis of pancreatic disease was verified in each of our patients by clinical studies, laboratory tests and radiological examinations. Only 40 per cent of these patients had steatorrhea. This, however, should not be taken as a true incidence of steatorrhea in pancreatic disease since only patients suspected of steatorrhea were studied.

Table IV shows the correlation of the I^{131} triolein test with the fecal chemical balance study in twelve patients suffering from chronic pancreatitis without steatorrhea. All had normal fecal fat; 92 per cent had normal fecal radioactivity, blood radioactivity was normal in 83 per cent. Thus there was an incidence of 8 and 17 per cent false positives by the fecal radioactivity and blood peak radioactivity tests, respectively. There was complete three-test agreement in 75 per cent of the cases.

Table IV shows the correlation of the I^{131} triolein test with fecal fat, determined chemically, in ten patients with chronic pancreatitis and "chemical" steatorrhea. All had abnormal fecal fat (by definition), 90 per cent had abnormal fecal radioactivity, only 60 per cent had abnormal blood peak radioactivity. There were 10 and 40 per cent false negatives by the fecal radioactivity and blood peak radioactivity tests, respectively. There was complete three-test agreement in six of the ten patients and complete disagreement in one.

From these results it is clear that the I^{131} triolein tests are not as sensitive an index of steatorrhea in disease of the pancreas as is the chemical determination of fecal fat. The fecal

TABLE IV

NORMAL AND ABNORMAL RESULTS BY THREE TESTS IN THE VARIOUS GROUPS OF PATIENTS

Subjects (no.)	Fecal (Chemical) Fat				Fecal Radioactivity				Blood Peak Radioactivity			
	Normal (7 gm./day or less)		Abnormal (7 gm./day or more)		Normal (7% or less)		Abnormal (more than 7%)		Normal (9% or more)		Abnormal (less than 9%)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Untreated idiopathic steatorrhea (11)	0	0	11	100	2	17	9	83	2	17	9	83
Treated idiopathic steatorrhea (4)	2	50	2	50	2	50	2	50	3	75	1	25
Acute pancreatitis (3)	3	100	0	0	3	100	0	0	2	66	1	33
Chronic pancreatitis without steatorrhea (12)	12	100	0	0	11	92	1	8	10	83	2	17
Chronic pancreatitis with steatorrhea (10)	0	0	10	100	1	10	9	90	4	40	6	60

radioactivity determination is, however, a much better index than blood peak radioactivity determination.

Table II shows, in summary, the mean fecal wet weight, with the standard deviation in different groups. Attention is called to the last column which shows the differences from the normal control group. The "p" value was significant in all.

Table II summarizes the mean fecal dry weight, in standard deviations in different groups. It was significantly abnormal only in patients suffering from idiopathic steatorrhea who were not treated and in patients suffering from chronic pancreatitis with steatorrhea, the "p" value for both being less than 0.001. Table II also shows the mean values with standard deviations, of fecal fat expressed as percentage of the fecal dry weight. This was statistically significant only in the untreated group with idiopathic steatorrhea, the "p" value for this group being less than 0.001. In Table II the mean fecal (chemical) fat values, expressed as grams per day, with standard deviations, are also summarized. The mean fecal fat values were significantly different from the normal in untreated patients with idiopathic steatorrhea, treated patients with idiopathic steatorrhea, and in patients suffering from chronic pancreatitis with steatorrhea, the "p" values being less than 0.001, less than 0.01, and less than 0.001, respectively. It was not statistically significant in patients suffering from chronic pancreatitis without steatorrhea and also probably not significant in patients suffering from acute pancreatitis. Table II further shows the mean fecal nitrogen values, with standard deviations in different groups. The mean fecal nitrogen was significantly abnormal in the untreated group with idiopathic steatorrhea and in patients suffering from chronic pancreatitis with steatorrhea. It probably was not significantly abnormal in the other groups.

The mean fecal radioactivity values, with standard deviations in different groups, are shown in Table II. The differences from normal were statistically significant in the patients with idiopathic steatorrhea and in the patients suffering from chronic pancreatitis with steatorrhea. They were not significant in patients suffering from chronic pancreatitis without steatorrhea and also probably not significant in patients suffering from acute pancreatitis. Table II further lists the mean blood peak radioactivity values with standard deviations in different groups. The differences from normal were statistically significant in all except those with acute

pancreatitis. The mean values in patients with idiopathic steatorrhea who were treated and in patients suffering from chronic pancreatitis without steatorrhea were above the calculated lower limit of normal but still statistically different from the normal. The mean fecal wet weight was much higher in patients suffering from idiopathic steatorrhea than in patients suffering from chronic pancreatitis with steatorrhea; the mean fecal dry weight in both groups of patients was nearly the same. This difference may be due to an increased water content in the stools of patients suffering from idiopathic steatorrhea. The mean fecal fat, expressed as grams per day and also as percentage of dry weight, was higher in patients suffering from idiopathic steatorrhea than in patients suffering from chronic pancreatitis with steatorrhea. On the other hand, the mean fecal nitrogen was higher in patients suffering from chronic pancreatitis with steatorrhea than in patients suffering from idiopathic steatorrhea, although the range in both groups was about the same. The mean fecal radioactivity value after the I^{131}-labeled triolein meal was also somewhat higher in patients suffering from idiopathic steatorrhea. The mean blood peak radioactivity after the I^{131}-labeled triolein meal was nearly the same in both groups.

We cannot differentiate between pancreatic and idiopathic steatorrhea on the basis of any of these values. Table IV shows in summary the results in all groups. When this table is analyzed, certain interesting observations become obvious. In each group, more fecal fat chemical determinations were abnormal, an intermediate number of fecal radioactivity determinations were abnormal, and least of the blood peak radioactivity determinations were abnormal. Of the fecal and blood peak radioactivity determinations, the fecal radioactivity study showed a better correlation with the chemical determination of fecal fat.

It would therefore appear that about a fourth to a half of the patients with steatorrhea would have been considered falsely to be normal by fecal radioactivity and blood peak radioactivity tests, respectively, while about a fifth to a fourth of those with normal fecal (chemical) fat would have been falsely called abnormal by fecal radioactivity and blood peak radioactivity tests, respectively. When both fecal and blood radioactivity are taken into consideration, about 75 per cent of the results are consistently abnormal while about 80 to 95 per cent of the results are consistently normal. The accuracy of the I^{131} triolein test, when both fecal and blood peak radioactivity is determined, is about 85 per cent whereas when only blood radioactivity is determined it is only about 50 to 60 per cent.

The use of radioiodinated (I^{131}) fat in the investigation of digestion and absorption involves some important sources of error. It must be remembered that the fat being used is not usually present in such amounts in the diet. The iodine is partly split off from the organic compound both in the intestinal content by the action of bacterial enzymes and in the cells after absorption. I^{131} exists in blood in two forms after the ingestion of labeled triolein. The bulk of the radioactivity is present as inorganic I^{131}; the remainder is bound to lipid. This lipid-bound I^{131} represents the ingested fat which is in transport in the blood as lipoprotein and chylomicrons. The lipid fraction usually contains 20 to 35 per cent of the whole blood radioactivity, with a range from 0 to 50 per cent. We have carried out several experiments not included in this report which confirm this finding.

The absorbed I^{131} is excreted mainly by the kidney as inorganic I^{131}. Beres et al. [*6*] found that normally the mean twenty-four-hour urinary excretion was 55 ± 11 per cent, with a range of 24 to 68 per cent. Since this I^{131} is in the form of inorganic iodide, the value represents the result of several metabolic processes: fat absorption, fat utilization, completeness of thyroid blockade, and renal excretion. Hence it is not possible to get quantitative information from blood activity studies alone as to the extent and rate of absorption, since both are influenced by the rate of elimination by the kidney. However, if the radioactivity in the blood is followed, valuable information may be obtained about the time relationships in absorption. Also, the inorganic I^{131} level is dependent upon the rate of utilization of the fat (at which time the iodine-fatty acid bond apparently is broken). Turner [*46*] demonstrated that in dogs, after feeding 20 gm. of a labeled fat meal, the changes in the plasma I^{131} lipid curves paralleled the changes in turbidity; but as the quantity of olive oil fed with I^{131}-labeled triolein was increased, there were changes in plasma turbidity and I^{131} lipid activity, the I^{131} lipid activity decreasing and the plasma turbidity increasing as the amount of fat was increased. This, however, was not observed in man [*28*]. Moreover, Turner [*46*] noted a differ-

ence between young and old dogs in their response to fat administered by the oral and intravenous routes. The plasma I^{131} lipid activity and turbidity after the ingestion of fat were more markedly increased in the old dogs as compared to the young dogs. The elevated levels were shown to be the result of an unexplained decrease in the rate of removal of fat from the blood in the old dogs. Van Handel and Zilversmit [*48*] studied the validity of I^{131}-labeling of fat by (1) comparing I^{131} lipid radioactivity with chemically determined fat in lymph and lipemic blood, and (2) mixing I^{131}-labeled fat or fatty acid with C^{14}-labeled fat or fatty acid and determining the ratio of the lipid I^{131} to the C^{14} in lymph fat and in the neutral fat and phospholipid fraction of tissues. These results confirmed Turner's observation that I^{131}-labeled triolein administered intravenously as an emulsion disappears from the blood at the same rate as neutral fat. However, differences were found in the lymph. After the oral administration of I^{131}-labeled triolein, the concentration of I^{131} triglyceride in the dog plasma during the period of alimentary hyperlipemia was lower than that of the chemically determined fat. This difference between the specific activity of fed fat and plasma fat exists in lymph, as shown by the low specific activity of dog and rat lymph compared to that of the administered fat. Comparison of I^{131}- and C^{14}-labeled triolein showed that dilution by an endogenous triglyceride pool cannot account for the observed decrease in specific activity. These authors state that I^{131}-labeled triolein does not appear to give a quantitative measure of the amount of fat absorbed, no matter whether part of the I^{131} is broken off the fat or whether I^{131}-labeled triolein is absorbed at a rate different from triolein; but these authors believe that this finding does not necessarily affect the use of I^{131}-labeled triolein as an empirical clinical test for the malabsorption syndrome.

The question of the origin of fecal fat is not definitely settled. Hence, as far as the fecal analysis of radioactivity is concerned, the enterohepatic circulation of iodine, as well as the secretion of I^{131}, either as lipoprotein or inorganic I^{131}, into the gut should be taken into consideration. Beres et al. [*6*] report that only 0.5 per cent of the administered dose was recovered in a four-day collection of bile in a patient with biliary fistula. This is quite insignificant and may not affect the final fecal analysis of radioactivity. Whether there is any secretion of I^{131} lipid into the gastrointestinal tract remains to be determined.

If labeled fats are fed and the unabsorbed residue recovered from the feces, as a means of assessing the extent of defect in fat absorption, no one tracer would give a result equivalent to that obtained by the feeding and recovery of mixed dietary triglycerides, although several labeled fats given together might do so. The wide fluctuation over relatively short periods recorded in celiac disease indicates that single dose tests with tracers would be likely to give misleading results. For these reasons, French [*20*] concludes that the use of labeled fats for the general assessment of dietary fat absorption is not a satisfactory substitute for the continuous balance method.

Further, the sources of error by contamination of the feces with urine are very great in the I^{131} triolein test, since a large quantity of I^{131} is excreted in the first twenty-four-hour urine. If, by chance, the patient mixes even a small amount of urine with the stool, the fecal values will be markedly increased. In our study every effort was made to exclude this source of error. Moreover, in general, there were more false positive or false negative results with the blood peak radioactivity determinations than with fecal radioactivity determinations; this fact in itself speaks against any possible contamination of feces with urine. Also, fecal nitrogen was increased only when fecal fat also was increased. This may again indicate that there was no urinary contamination with feces in the majority of our tests.

CONCLUSIONS

Blood peak radioactivity, fecal radioactivity and fecal fat (chemical) studies were performed in ten patients suffering from idiopathic steatorrhea and twenty patients with diseases of the pancreas. The data were compared with the results obtained in twenty-four normal volunteer subjects.

In the untreated group with idiopathic steatorrhea, the fecal fat excretion was abnormal in all the patients. Both fecal radioactivity and blood peak radioactivity were abnormal in 83 per cent of the group. There was complete three-test agreement in 73 per cent while in the remaining 17 per cent one or both tests disagreed. There was a 17 per cent incidence of false negatives by the blood peak and fecal radioactivity tests.

The triolein test is not a good index of the presence of steatorrhea in patients suffering from idiopathic steatorrhea who are in clinical remission.

In the treated group with idiopathic steatorrhea the blood peak radioactivity tended to return to normal levels long before steatorrhea completely disappeared. Of the two determinations, the fecal radioactivity determination is a much better index of the presence of steatorrhea in the group with idiopathic steatorrhea than is the blood peak radioactivity determination.

In twelve patients with chronic pancreatitis without steatorrhea the fecal fat (chemical) was normal in the entire group; fecal radioactivity was within normal limits in 92 per cent of the patients; and blood peaks of radioactivity were normal in 83 per cent. There was complete three-test agreement in 75 per cent, while in the remaining 25 per cent one or both tests disagreed. There were 8 and 17 per cent false positives according to fecal and blood peak radioactivity tests, respectively. There were no false negatives in this group.

In ten patients with chronic pancreatitis with steatorrhea the fecal fat (chemical) was abnormal in all, abnormal fecal radioactivity was present in 90 per cent, abnormal blood radioactivity levels occurred in only 60 per cent. There were 10 and 40 per cent false negatives by the fecal and blood peak radioactivity tests, respectively.

From these results it may be concluded that, in general, in each group of patients with abnormal fecal fat excretion as chemically determined, the fecal radioactivity determination was abnormal in about 85 per cent while the blood peak radioactivity was abnormal in 72 per cent. On the other hand, in those who had a normal fecal fat excretion by chemical methods, nearly 80 to 90 per cent had both blood and fecal radioactivity in the range of normal. These results tend to suggest that the triolein test is likely to be normal in four-fifths of those who do not have steatorrhea while its accuracy in the presence of steatorrhea is about two-thirds to three-fourths. Also, the I^{131} triolein test does not give as quantitative an estimation of the degree of steatorrhea as does the fecal chemical balance. Of the two I^{131} triolein determinations, the fecal radioactivity study is a much better index of the presence of steatorrhea than is the blood peak radioactivity test. When both are determined the index of accuracy is still better.

Although the I^{131} triolein test is a good, simple, exploratory test for the detection of steatorrhea, particularly if both fecal and blood peak radioactivity are determined, our results show that it is not as sensitive in the detection of steatorrhea as the chemical determination of fecal fat.

If facilities for metabolic balance studies are not available, then, because of its simplicity, the triolein test (using both blood peak and fecal radioactivity determinations) may prove a useful substitute in the detection of steatorrhea, provided its limitations are fully appreciated.

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Clinicopathologic Conference

Staphylococcal Septicemia

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A TWENTY-ONE year old white male baker was admitted to the Barnes Hospital for the first time on October 12, 1959, with complaints of fever, chills, aches, malaise and bleeding from the mouth.

The patient had been in good health until one day prior to his admission when bleeding from his mouth, considered to be from the roof of the mouth, developed suddenly. Shortly thereafter shaking chills and fever developed. During the night he vomited two to three times. On the morning of admission the patient had continuous, non-pleuritic pain in the left anterior portion of his chest. He stated that he had had bleeding gums for two weeks prior to admission. There was no history of headache, sore throat, cough, shortness of breath or diarrhea. The patient's mother stated that he had had polydipsia and polyuria for a long time. Polydipsia and polyuria were reported also in the patient's mother and sister. His maternal grandmother had diabetes. The patient stated that he drank at least five bottles of beer a day. Additional history revealed that the patient had been quite inebriated on the night prior to admission. There was no history of recent dental extraction, rheumatic fever or other heart disease.

Physical examination revealed a temperature of 40.4°C., pulse 120 per minute, respirations 25 per minute, and a blood pressure of 120/75 mm. Hg. The conjunctivas were injected. There were diffuse wheezes over the base of both lungs and decreased breath sounds over the base of the right lung. The heart size was normal on physical examination. The rhythm was regular and there were no murmurs. Results of the abdominal examination were within normal limits.

The laboratory data were as follows: hemoglobin, 13.9 gm. per cent; white blood cell count 16,250 per cu. mm. with a differential percentage of 3 juveniles, 18 stab forms, 73 segmented neutrophils, 2 lymphocytes and 4 monocytes. Urinalysis showed a specific gravity of 1.030; albumin and sugar negative; 18 to 20 white blood cells and 5 to 6 red blood cells per high power field. Stool guaiac and cardiolipin reaction were negative. The C-reactive protein was 2 plus. The antistreptolysin 0 titer was 25 units; cold and heterophil agglutinations were negative. Salmonella typhi O, group C and group E agglutinins were negative, as were brucella agglutinins. The serum phosphorus was 2.1 mg. per cent. On October 16 stool guaiac reaction was positive. Fasting blood sugar was 134 mg. per cent; cholesterol, 113 mg. per cent; and the reticulocyte count, 1 per cent. On December 30 a twenty-four-hour urine specimen showed no protein; volume was 3,600 cc.; sodium, 27 mEq. per L.; potassium, 12.4 mEq. per L.; and chloride, 36 mEq. per L. The serum calcium was 9 mg. per cent and phosphorus was 5.4 mg. per cent. Additional laboratory data appear in Tables I and II.

During the patient's prolonged hospital stay, he remained febrile with temperatures ranging from 38° to 40°C. A blood culture obtained on admission grew out coagulase-positive Staphylococcus aureus, as did six others between admission and December 8. Roentgenograms of the chest showed only calcification of hilar nodes. Penicillin, streptomycin and erythromycin therapy were started but the sensitivity studies on the organism revealed resistance to erythromycin and sensitivity to novobiocin. Hence, erythromycin therapy was cancelled and novobiocin was started.

Two days after admission pustules were noted over the extremities and one hemorrhage was noted in the left conjunctiva. A chest roentgenogram revealed pneumonitis of the posterior portion of the lower lobe of the left lung, and minimal left ventricular enlargement. A sputum

TABLE I
SUMMARY LABORATORY DATA

Date	Hemoglobin (gm. %)	White Blood Cell Count (per cu. mm.)	Blood Urea Nitrogen (mg. %)	Serum Electrolytes (mEq./L.)				Alkaline Phosphatase (Bodansky units)	Cephalin Flocculation	Bromsulfalein Retention (%)
				Sodium	Potassium	Carbon Dioxide	Chloride			
10/12/59	13.9	16,250	17	...	...	...	...	...	...	...
10/13/59	...	...	...	...	...	...	...	2.6	Negative	...
10/16/59	...	...	...	...	...	...	...	...	...	12.5
10/26/59	...	...	15	...	...	...	...	...	Trace	...
10/28/59	11.4	8,650	...	...	...	...	...	...	...	...
11/7/59	10.2	14,300	...	...	...	...	...	...	...	...
11/12/59	...	...	...	...	...	...	...	14	...	...
11/16/59	...	...	...	125	4.2	24.8	90	...	...	16
11/21/59	7.9	10,050	...	...	...	...	...	...	...	...
11/23/59	...	...	14	132	4.3	21.9	102	20.2	...	...
12/2/59	9.7	...	...	126	4.1	21.9	96	23.4	3 plus	...
12/21/59	9.7	5,400	21	131	4.2	25.5	94	...	...	...
12/26/59	8.3	6,800	36	140	3.4	21.9	95	...	...	...
12/29/59	9.5	15,650	47	109	4.3	15.6	82	...	...	...
1/2/60	9.7	28,000	53	124	4.6	14.3	97	...	...	...
1/4/60	8.3	7,650	74	130	4.2	20.2	95	...	...	...

culture grew hemolytic, coagulase-positive Staph. aureus. At this time the patient complained of pain and tenderness of the left knee. Roentgenograms of the left knee did not reveal any abnormalities, and within four days the tenderness disappeared. A glucose tolerance test was performed and revealed a diabetic-type curve.

During the second week of hospitalization the patient's temperature ranged between 37° and 38°c., one of only two periods during hospitalization when the patient was afebrile. Sputum culture grew mycelia, penicillium and Candida albicans; three days later it grew aerobacter and klebsiella. A urine culture grew aerobacter. The administration of penicillin and novobiocin was stopped because the organism in the blood had developed resistance to these drugs. One day later new petechiae were noted in the right conjunctiva. Therapy with kanamycin and vancomycin was started. On October 31 an apical systolic murmur was noted. One week later pain, tenderness and swelling of the left ankle and foot developed. Roentgenograms of the foot did not reveal any abnormalities. On November 8 ristocetin was added to the therapeutic regimen. A surgical consultation was obtained three days later because of sudden onset of abdominal pain, nausea and vomiting. It was thought that the patient probably had a gastroenteritis, but mesenteric thrombosis was considered a possibility. An electrocardiogram at this time was consistent with a metabolic or toxic disturbance. Chest roentgenograms on November 14 were interpreted as showing an increase in the pneumonia in the lower lobe of the left lung.

Two and a half weeks after the heart murmur

TABLE II
BLOOD CULTURES*

Date	Growth in Broth	Growth in Plates (colonies per ml.)
October 12	+	25
October 21	−	None
October 23	+	1–2
October 25	+	126
November 20	+	Too numerous to count
December 8	+	−
December 11	−	None
December 15	−	None
December 21	−	None
December 28	−	None
January 4	−	None

* Non-hemolytic Staphylococcus aureus, coagulase-positive, phage type 80/81.

was first heard, a pulsation was noted in the third left intercostal space. In addition, diastolic and systolic murmurs were heard in the pulmonic area. The patient continued to show petechiae in the conjunctivas and splinter hemorrhages developed under the nails. Chest roentgenograms showed interval increases in the size of the pulmonary outflow tract, pulmonary artery and peripheral pulmonary artery, with a marked decrease in the size of the aortic knob. These findings were considered compatible with spontaneous rupture of the aorta into the pulmonary artery. A right heart catheterization was performed. There was no evidence of a left-to-right shunt; only slightly elevated pulmonary and right ventricular pressures were noted. Shortly after the cardiac catheterization a shaking chill and new conjunctival hemorrhages developed.

Two months after admission a liver biopsy specimen was obtained which showed acute focal inflammation. Because of progressive dyspnea and a roentgenographic diagnosis on the previous day of pulmonary edema, the patient was digitalized and given diuretics. On December 23 the patient became lethargic and confused. An electrocardiogram on this day showed left ventricular enlargement, digitalis effect and changes compatible with electrolyte imbalance. Within three days anorexia and vomiting occurred. At this time an electrocardiogram showed frequent ventricular premature contractions with bigemini and multifocal ventricular premature contractions. The question of digitalis intoxication was raised. Potassium therapy was given. Respirations became more labored and the patient required oxygen. Dyspnea and orthopnea became progressively more severe and edema of the feet and ankles developed. The pulmonic second sound gradually increased in intensity. A blood culture showed no growth. On December 29 thrombophlebitis developed in the arm, secondary to intravenous medication.

From January 1 until death the patient's temperature varied from 36.7° to 37.3°C. On the day before death diffuse gurgling rales and wheezes were heard throughout both lung fields, and an electrocardiogram was interpreted as showing sinus tachycardia, anterolateral subendocardial myocardial injury and/or digitalis effect. On the same day chest roentgenograms revealed pulmonary edema. On January 5 the house officer was summoned because the patient had had precordial pain while eating breakfast. By the time the house officer arrived the patient had died.

CLINICAL DISCUSSION

Dr. Edward H. Reinhard: The patient under discussion was a twenty-one year old man who, aside from a history of binge drinking, was well until the acute onset of fever, chills and bleeding from the mouth. He had had no previous rheumatic fever or other known heart disease. He had no heart murmurs on admission.

Dr. McAlister, could you discuss the roentgenograms of the chest taken on admission?

Dr. William H. McAlister: The bony thorax appeared normal without evidence of rib-notching. The pulmonary artery was a bit prominent, but I believe it was within normal limits. The pulmonary vascularity appeared normal. There was a small infiltrate in the lower lobe of the right lung.

Dr. Reinhard: A blood culture obtained on admission was found, two days later, to have a heavy growth of yellow coagulase-positive staphylococcus in the broth and in both pour plates. At this time the diagnosis of staphylococcal endocarditis was entertained, and during the patient's stay in the hospital this diagnosis became more and more apparent. Dr. Walsh, in this patient murmurs developed later in the course of his hospital stay. Is the staphylococcus apt to attack a normal heart valve? Do you think that we have to assume that he had a nonapparent rheumatic endocarditis?

Dr. James W. Walsh: In contrast to subacute bacterial endocarditis, in acute endocarditis due to the staphylococcus it is expected that the heart valve involved will be one which has previously been completely undamaged.

Dr. Reinhard: If a patient has a staphylococcal septicemia, whether or not the bacteria settle on the heart valve is purely fortuitous. Dr. Kingsland, does the staphylococcus have any special predilection for any of the heart valves? Is one side of the heart more frequently involved than the other?

Dr. Robert C. Kingsland: This infection appears mainly on the left side of the heart, and I will say that is the more frequent localization.

Dr. Reinhard: Dr. Walsh, what valve do you think was involved here?

Dr. Walsh: I think the patient's course and physical findings, together with the various procedures that were carried out, favor involvement of the mitral valve.

DR. REINHARD: Dr. Kingsland, do you want to comment on any special characteristics of staphylococcal endocarditis in terms of the effect of the bacteria on the valves?

DR. KINGSLAND: This is a very damaging organism. Great defects are produced in the valve, with perforation and deformity, usually leading to hemodynamic difficulties.

DR. REINHARD: Dr. McAlister, would you discuss the remainder of the chest roentgenograms?

DR. MCALISTER: A chest roentgenogram taken four days after admission exhibited little change in the cardiac size. The pulmonary vascularity again appeared normal. The infiltrate in the lower lobe of the right lobe had largely cleared. A small segmental area of atelectasis had appeared in the lower lobe of the left lung. Four weeks after admission the heart size was a little larger; this was in part related to expiration. There was progression of the disease in the lower lobe of the left lung. One week later the chest exhibited some improvement in the infiltrate. The heart became larger and there was evidence of dilated pulmonary veins. One week later, or two months after admission, the chest roentgenogram showed frank congestive failure, with pulmonary edema. There was a pleural effusion on the left, which again would bring up the possibility of pulmonary infarction on the left. A little over one week later the heart size had decreased somewhat. I would interpret these findings as representing pulmonary venous congestion rather than arterial over-circulation.

A chest roentgenogram taken one day prior to death showed the heart to be enlarged with extensive pulmonary edema greater on the right. Interestingly enough, there had been some clearing of the segmental areas of infiltrate that we saw on the left.

DR. REINHARD: It would certainly appear that this patient had, at the time of admission to the hospital, an inflammatory process in the lower lobe of the left lung. During the course of his hospitalization obvious heart failure developed. However, the inflammatory process in the lung appeared to clear. This patient, I believe, had an infection of the lung initially. I believe it was probably staphylococcal. An endocarditis due to the staphylococcus then developed, and the question is: Was the lesion in the lung embolic from the heart valve, or was the lesion on the valve secondary to a septicemia associated with the pneumonia? Dr. Goldman, what do you think?

DR. ALFRED GOLDMAN: The history would suggest that he had the lesion in the lung first. However, there was evidence that he probably had an endocarditis, so I think it would be difficult for me to state definitely which came first.

DR. REINHARD: I am asking you these leading questions because, if endocarditis did not come from the lung lesion, we are left without explanation as to the portal of entry.

DR. GOLDMAN: That is right.

DR. REINHARD: I would like to emphasize that in this case the lung is a likely port of entry.

DR. GOLDMAN: This is highly probable.

DR. REINHARD: You saw the patient in the hospital, Dr. Harford, and I believe you thought that the lung lesion came first and represented the portal of entry to the bacteria. Is that correct?

DR. CARL G. HARFORD: That is correct, but it cannot be proved. Nevertheless, the fact that the patient had been on a binge of drinking the night before onset of his acute illness would support this idea. There is good experimental evidence to show that migration of phagocytic cells is impaired in animals that have been narcotized by alcohol or other drugs and that such animals have a greatly lowered resistance to pulmonary infection. The circumstances of this case appear to be similar.

DR. REINHARD: Is this mechanism more important than the older mechanism of paralysis of the ciliary function?

DR. HARFORD: Yes, I think the evidence is stronger. I do not know of evidence that shows that narcotization of intact animals causes paralysis of the ciliary mechanism. Several years ago I tried such experiments in mice and never succeeded in stopping ciliary beat.

DR. REINHARD: Does anyone else have any comments on this particular aspect of the case? Dr. Harford has been good enough to summarize the bacteriological data (Table II) for us. Would you discuss this now, Dr. Harford?

DR. HARFORD: Although other kinds of cultures were taken, I recorded only the blood cultures here because they were the most significant. In bacterial endocarditis, it has seemed to me that post-treatment blood cultures are of extreme importance because the persistence of positive cultures indicates that treatment is failing. In the present case, the first blood culture after the institution of therapy was negative; but

after that small numbers of bacteria appeared again and on November 20 there were so many that their number could not be counted in the poured plates, probably 500 to 1,000 per ml. Blood cultures were still weakly positive on December 8, but after that five consecutive blood cultures were negative, including one taken the day before death. These negative cultures may be important.

Sensitivity tests of the organism *in vitro* showed growth in 50 units of penicillin per ml., but no growth in 1 μg. per ml. of vancomycin and kanamycin and no growth in 1 unit of bacitracin per ml. There was growth in 50 μg. of erythromycin per ml. There was no growth in 5 μg. per ml. of ristocetin. Initially, there was failure of growth in 1 μg. per ml. of novobiocin, but later growth occurred in 50 μg. per ml. of this substance.

DR. REINHARD: Will you discuss the problem of the treatment the patient actually received, and any suggestions or criticism you might have of this treatment?

DR. HARFORD: Staphylococci from the blood of this patient were resistant to penicillin, and since penicillin is the most important drug for the treatment of bacterial endocarditis of most types, it was a tremendous handicap not to be able to rely upon it.

Vancomycin was used because it is a potent antistaphylococcal drug and also is bactericidal. Vancomycin therapy was discontinued on December 8 because the blood cultures were still positive. The patient also received ristocetin, but this drug would be less likely to be effective in bacterial endocarditis because its action is usually bacteriostatic. Bacitracin was used especially during the last part of the illness, and may have had some eradicative action because it is a bactericidal drug.

DR. REINHARD: What Dr. Harford has reviewed here is very important, because from reading the protocol one might obtain the impression that the treatment was not really effective in this case, perhaps not effective at all. Actually, treatment was at least markedly suppressive, if not obviously curative. Would you agree?

DR. HARFORD: Yes. While a positive blood culture shows that treatment is failing, a negative blood culture does not necessarily indicate success since active infection within vegetations may persist with negative blood cultures.

DR. REINHARD: When the bacterial colony count decreases, is this significant? Does this indicate that you are really suppressing the infection or is this very variable?

DR. HARFORD: In bacterial endocarditis caused by Streptococcus viridans, I think that the evidence shows the numbers of bacteria in the blood to be remarkably constant. Decreased numbers might indicate some therapeutic effect, but I think that persistence of any bacteria in the blood are indicative of failure.

DR. REINHARD: During the first month that the patient was in the hospital he had several minor episodes of abdominal discomfort and nausea; the first few episodes apparently cleared up spontaneously. The third episode started about a month after admission to the hospital, with nausea, vomiting and generalized abdominal pain. These symptoms persisted all night. They were of such severity that the patient was seen by a surgical consultant, who described the abdomen as soft with hyperactive bowel sounds. There were no masses and no muscle guarding. There was at that time a city-wide epidemic of gastroenteritis, and he was inclined to think that this episode probably was a viral gastroenteritis. He mentioned, however, the possibility of a septic embolus to some of the structures in the abdominal cavity perhaps the intestine. I suppose we really cannot go much further than this.

Dr. Kingsland, I would like to ask if you think there was any evidence that this patient had any peripheral emboli, and if so, does this help us in localizing the site of valvular vegetation?

DR. KINGSLAND: Petechiae in the conjunctivas and under the nails were described. Now, unless somebody is misinterpreting these, I consider this evidence of embolism. I would not say that this indicates anything more than probable valve involvement in the left side of the heart. It is difficult to eliminate septic emboli to the mesenteric vessels. However, there was not much evidence that an actively important lesion in the abdomen developed, at least not from the viewpoint of muscle guard, severe tenderness or development of further signs suggesting intestinal obstruction.

DR. REINHARD: We will now take up one of the most interesting aspects of this case. No heart murmurs were heard by anyone during the first two and a half weeks that the patient was in the hospital. Then an apical systolic murmur developed which over a period of four or five days

appeared to become progressively harsher and more high-pitched. Perhaps the murmur then changed little in character for the next two weeks (at least no further mention was made of any change in the character of the murmur). Then rather suddenly some striking changes were noted. At this time the pulmonic second sound and the aortic second sound were described as very loud, and the systolic murmur, which had been present for a little over two weeks, now became very much harsher. In addition, a definite decrescendo diastolic murmur appeared. At this time the patient was having obvious embolic phenomena, including splinter hemorrhages of the fingers and conjunctival hemorrhages.

Dr. Walsh, what might account for the development of these murmurs and the ensuing changes?

DR. WALSH: I think the most likely explanations might be rupture of a papillary muscle, chordae tendinae, a heart valve or the development of an aneurysm of the sinus of Valsalva.

DR. REINHARD: Dr. McAlister, the chest films taken on November 21 were interpreted officially as showing an interval increase in the pulmonary outflow tract, the pulmonary artery and the peripheral branch of the pulmonary artery, with a marked decrease in the size of the aortic knob. These findings were considered suggestive of spontaneous rupture of the aorta into the pulmonary artery. The validity of this interpretation is open to serious question because of the impossibility of being sure that the engorged vasculature in the lung was arterial rather than venous. If it was venous, of course, it could all be due to cardiac failure, and indeed you have already taken this latter position. I wonder if you would comment on the radiologic diagnosis of aortic sinus rupture?

DR. MCALISTER: Since the aortic sinuses are intracardiac structures, considerable dilatation may not be detected on plain roentgenograms. Roentgenographic findings of associated conditions, such as coarctation or syphilitic aortitis may be present. In the latter, calcification in the ascending aorta may extend down and outline the aortic sinus aneurysm. In addition to calcification in the wall of the aneurysm, there may be thrombus calcification. This ring-like calcification has often been confused with that seen in the left atrial wall. Fluoroscopy may help demonstrate a bulge from the cardiac contour. If rupture occurs into the right side of the heart or pulmonary artery there may be expansile pulsations of the pulmonary artery in addition to pulmonary over-circulation. In general, all that one sees in rupture of the aortic sinus aneurysm is a progressive cardiac enlargement, and the exact chamber or chambers which are enlarged depend in part on where the rupture occurs. One cannot predict the cardiac chamber the aneurysm will rupture into. Thoracic aortography is the best means of demonstrating the anatomic relationships and also the communication.

DR. REINHARD: Dr. Parker, you performed right heart catheterization studies on this patient in an attempt to elucidate the problem. Would you discuss the results and tell us if you think this was fairly conclusive in excluding rupture of the sinus of Valsalva?

DR. BRENT M. PARKER: The results of the catheterization were negative. There was no evidence of a left-to-right shunt at any level. The pulmonary artery pressure was 35 mm. Hg systolic, which is slightly elevated, and this could have been due to left heart failure. In view of the roentgenographic changes, the location of the murmurs and the increasing loudness of the second pulmonic sound suggesting that if a shunt were present it was from left to right at the pulmonary artery or right ventricular level, these data would be rather conclusive in excluding a ruptured aortic sinus aneurysm. (Aortic sinus and sinus of Valsalva are synonomous terms.)

Congenital aneurysms of the sinus of Valsalva nearly always involve either the right aortic sinus or the non-coronary aortic sinus, and usually rupture into the right atrium or right ventricle. Acquired aneurysms may more often involve the left aortic sinus. When the left sinus is involved rupture may occur into the left side of the heart, or even, rarely, into the pericardium. Bacterial endocarditis may involve the aortic sinuses in congenital lesions, making it difficult to ascertain whether or not the sinus aneurysm was due initially to a congenital malformation or to the bacterial endocarditis. Bristow* has recently reported a case in which there was rheumatic aortic valve disease with staphylococcus endocarditis and finally development of erosion through the wall of the sinus of Valsalva and fatal rupture into the pericardium.

* BRISTOW, J. D., PARKER, B. and HAUG, W. Hemopericardium following rupture of a bacterial aortic sinus aneurysm. *Am. J. Cardiol.*, 6: 355, 1960.

Only twenty-one cases of bacterial endocarditis with ruptured aortic sinus on an acquired basis have been reported.

DR. REINHARD: Do you believe that we can exclude this diagnosis in this case?

DR. PARKER: Yes.

DR. REINHARD: Would you say that catheterization is more precise in excluding this diagnosis than angiography?

DR. PARKER: No, I believe aortography would be the most precise method of excluding this diagnosis. However, we consider this procedure to be somewhat more complicated and believe that it is perhaps attended by a slightly greater risk. Moreover, in this instance we were also considering other remote possibilities, such as patent ductus and ventricular septal defect, which could be diagnosed by right heart catheterization. We were looking for a treatable lesion which might have been repaired surgically.

DR. REINHARD: Dr. Kingsland, what did cause these sudden changes in murmurs, then? Are we left with the rupture of the valve or of the chordae tendinae?

DR. KINGSLAND: I think the most likely possibility is endocarditis involving the heart valve. We do not have to postulate a rupture of a sinus of Valsalva, chordae tendinae or valve. However, I think actual perforation or rupture of the valve, or gross deformity of the valve, is very likely.

DR. REINHARD: The rather dramatic appearance of the murmurs would be more in favor of necrosis with an actual perforation or rupture of the valve, would it not, than just a progressively increasing vegetation?

DR. KINGSLAND: I think that is so, except that two weeks elapsed before any murmurs were heard; at a time when there was some supposition that endocarditis was already there.

DR. REINHARD: A biopsy specimen of this patient's liver showed focal acute inflammatory lesions without abscess formation, considered compatible with the existence of a septicemia. The absence of abscess formation could be a time factor, or could be associated with the suppressive effects of chemotherapy. I think we can leave the hepatic problem without further comment.

The obvious explanation for the hematuria and the terminal azotemia would seem to be focal embolic glomerulonephritis. Dr. Morrin, would you discuss this problem?

DR. PETER A. F. MORRIN: This is a very good possibility, Dr. Reinhard. I might take exception to the use of the word embolic. Many people believe that this is probably not an embolic lesion, but is due to local necrosis in the glomeruli, attributed by some to an allergic or toxic etiology. It should be mentioned, however, that acute diffuse glomerulonephritis has been frequently reported in bacterial endocarditis, and Christian* gave an incidence of 80 per cent. This seems to be excessively high to us, but the lesion certainly does occur frequently. Another common event in these cases is infarction. It should be considered that this patient was receiving bacitracin, and also kanamycin, both of which are known to have some nephotoxicity.

DR. REINHARD: What kind of lesions do these drugs produce?

DR. MORRIN: They may produce a decrease in filtration rate, impaired tubular function and albuminuria. The histologic changes in man are not well documented, but in animals they are similar to those produced by other nephrotoxins such as heavy metals. In this case the pre-terminal rise in blood urea nitrogen may be attributable to cardiac failure rather than to further loss of functioning renal tissue.

DR. REINHARD: This patient's terminal course was certainly characterized by profound cardiac failure, associated with the obvious endocarditis. I do not believe there is anything particular to comment upon in the management of the cardiac failure. Dr. Harford, any other comments?

DR. HARFORD: I think that cardiac failure in bacterial endocarditis is more apt to occur with lesions of the aortic valve than with lesions of the mitral valve.

DR. REINHARD: Statistically speaking, however, lesions of the mitral valve with staphylococcal endocarditis are more common.

DR. WALSH: The mitral valve is involved in about 55 per cent of cases, the aortic in about 24 per cent, with 17 per cent for the tricuspid and about 4 per cent for the pulmonic valve.

DR. REINHARD: I think we can proceed to the final diagnosis. I believe this patient almost certainly had a bacterial endocarditis due to the Staph. aureus, secondary to a staphylococcal lung infection. I believe that the postmortem examination will show focal areas of staphylococcal infection in the liver, possibly in the kidneys, with perhaps the changes of focal glomerulonephritis. I believe the patient probably had a

* CHRISTIAN, H. A. The kidneys in subacute streptococcus viridans endocarditis. *J. Mt. Sinai Hospital*, 8: 427, 1942.

rupture of a valve and would be inclined to place this on the aortic valve. We can be reasonably confident that this was an endocarditis on the left side of the heart.

PATHOLOGIC DISCUSSION

DR. ROBERT M. O'NEAL: The clinical discussion has been very appropos and there will not be any big surprises for you.

Figure 1 is a view of the opened heart looking into the left atrium toward the anterior leaflet of the mitral valve. A large ulcerated defect of the valve was present; acute staphylococcic endocarditis had destroyed about half of the posterior leaflet and was encroaching on the anterior leaflet. There was no evidence of any previous valvular disease, the remainder of the mitral valve, as well as the other heart valves, appeared quite normal.

The edge of the valve at the site of the endocarditis was relatively normal, but granulation tissue was growing into the ballooning vegetation at the edge of the ulceration and layered fibrin formed the bulbous border. (Fig. 2.) The degree of granulation tissue ingrowth is certainly consistent with the prolonged clinical course of the patient's disease. The tip of the vegetation was especially interesting because there was absolutely no evidence of bacterial colonization there, indicating that an uninfected thrombus had been deposited over the bacterial vegetation. Within the deeper parts of the vegetation were "ghosts" of clustered cocci which were only faintly gram-positive. Since the vegetation was not cultured, we cannot eliminate the possibility that viable organisms were present deep within the vegetation, but cultures from the blood and many other parts of the body showed no growth. The heart weighed 450 gm., which is quite enlarged. It is unlikely that such a degree of hypertrophy occurred during this short illness, and no other evidence of hypertension was present. The best explanation for the increased heart weight appears to be the multiple small infarcts found throughout the myocardium. (Fig. 3.) The reaction to these infarcts, the results of showers of thromboemboli, probably accounted for the increase in heart size. The small infarcts were quite extensive, and occupied a good proportion of the wall of the left ventricle. Most of them appeared to be a little over two weeks of age with dropping out of the muscle fibers, some macrophages, but no acute cellular reaction. There may well have been some generalized tendency to thrombosis in this patient because even in the right atrium there was a mural thrombus overlying the endocardium. (Fig. 4.) This was not very recent, since there was organization in its base. The age of the thrombus suggests that right heart catheterization five weeks previously might have provided the local lesion over which the thrombus formed. There was no evidence that any emboli from this had reached the lungs.

The spleen contained multiple large infarcts, some organizing (Fig. 5) and some appearing more recent. The cause of these was readily found. The entire splenic artery was occluded by a large thrombus, almost certainly embolic from the mitral vegetation. The thrombus appeared fairly recent at one point, but almost completely organized at other points. (Fig. 6.) This thromboembolus was of considerable age, and might very well have been the cause of the acute episode of abdominal pain two months previously.

DR. REINHARD: Were there any inflammatory changes in the wall of the splenic artery?

DR. O'NEAL: None at all. The embolus probably arose from the tip of the mitral vegetation, which was essentially free of bacteria.

DR. REINHARD: Was there significant arteriosclerosis?

DR. O'NEAL: No, arteriosclerosis was extremely slight, even in the abdominal aorta.

The kidneys also contained numerous infarcts, none of which appeared to be infected. (Fig. 7.) Some of them were recent and some fairly old. The artery to the upper pole of the left kidney was occluded by a recent thrombus, and there was a recent infarct of that entire pole. From the protocol I gather that over half of both kidneys were infarcted, which explains the terminal uremia.

The condition of the brain was interesting, especially since the patient had no symptoms particularly related to it. Over the left frontal lobe there was an area of discoloration, and beneath this an abscess 3 cm. in diameter was found. This abscess was also of several weeks' duration, having a thick, well formed wall of connective tissue. Necrotic material occupied the center of the abscess, but no bacteria were identified. Also scattered through the brain, of which we had numerous sections, were many small emboli occluding arterioles. These looked very much like the tip of the vegetation that we saw on the mitral valve.

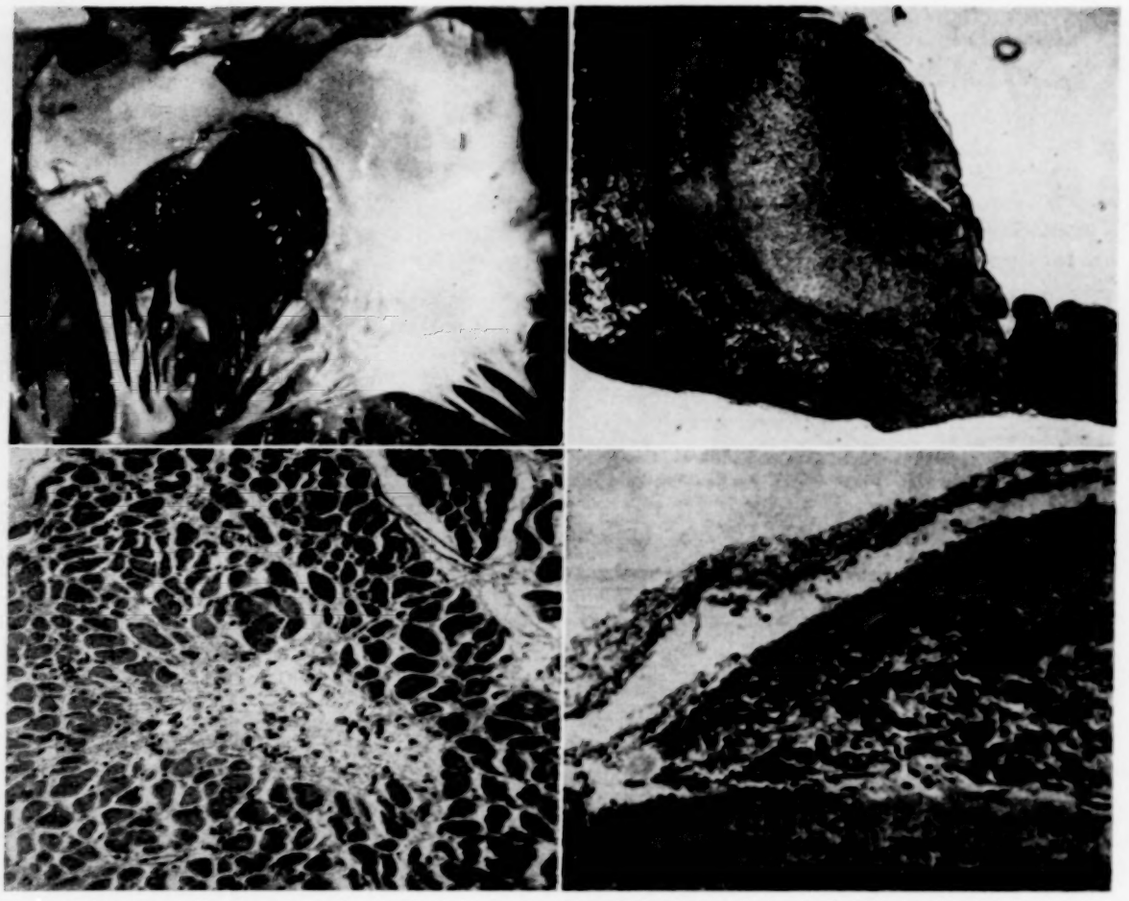

FIG. 1. Gross photograph of the heart. This view is of the mitral valve, with the anterior leaflet at the right. The large semicircular defect to the left of the anterior leaflet is characteristic of the destruction occurring in staphylococcic endocarditis. Dark, thrombotic vegetations are present at the edges of the ulcer.

FIG. 2. Low power photomicrograph of the edge of the ulcer, with layered fibrin overlying the organizing base of the ulcerated lesion. Hematoxylin and eosin stain, original magnification × 100.

FIG. 3. A small infarct of the myocardium typical of the many scattered through the heart muscle. Muscle cells have disappeared and the acute inflammatory reaction has subsided. Hematoxylin and eosin stain, original magnification × 100.

FIG. 4. The thrombus on the right atrial wall. The endocardium below appears normal. Fibroblasts have invaded between the coarse strands of fibrin, separating them. Hematoxylin and eosin stain, original magnification × 100.

The lungs were also quite interesting. There was 600 cc. of fluid in the left pleural cavity and 500 cc. in the right, consistent with the presence of left ventricular failure. The lungs contained no localizing lesions that would be consistent with a staphylococcal pneumonia, either old or recent; there was no evidence of an old necrotizing lesion or focal infection to indicate a site of origin for the patient's staphylococcic septicemia. The changes found were very uniform throughout all the areas of the lungs. There was much fibrin in alveoli, some thickening and cellular infiltration of alveolar walls, prominence of the alveolar lining cells, and numerous macrophages within the air spaces. (Fig. 8.) This is quite consistent with what we find so commonly in uremia, probably the result of widespread damage to capillary walls. Our interpretation is that the changes accompanying uremia were superimposed on those of passive congestion in the lung, exaggerating the effect of both.

In addition to the large abscess in the brain, one of similar appearance was found near the bifurcation of the aorta in the retroperitoneal space. But most of the lesions were due to uninfected thromboemboli which caused infarcts

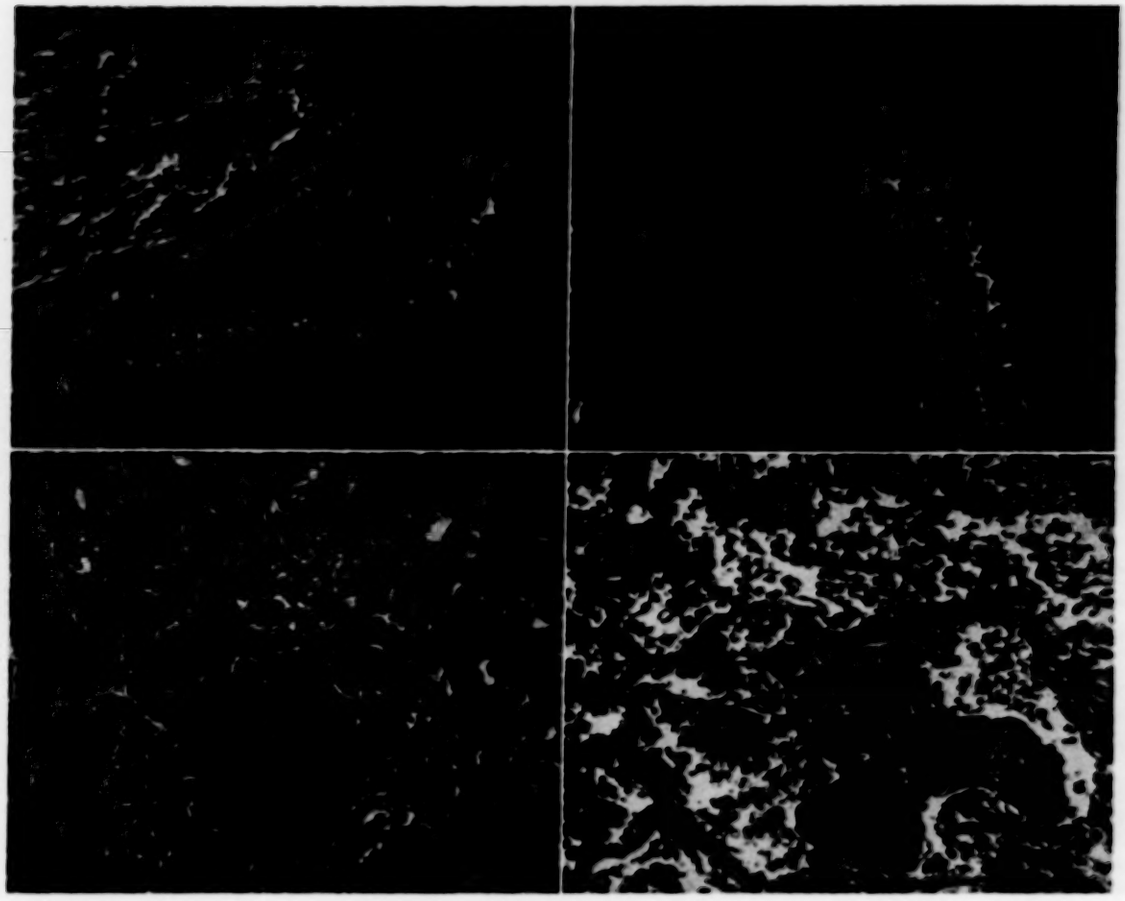

FIG. 5. The wall of a splenic infarct (*above*) is composed of fibrous tissue and the contents of the central portion of the infarct (*below*) are simply ghosts of splenic tissue. No evidence of infection is seen. Hematoxylin and eosin stain, original magnification × 100.

FIG. 6. The muscular wall of the splenic artery (right) appears perfectly normal. The occlusive thrombus was almost completely organized at this point, but the darker material at left center is residual fibrin. Hematoxylin and eosin stain, original magnification × 100.

FIG. 7. The border of a renal infarct with ghosts of tubules in the infarcted area (*lower left*) and only slight fibrosis at its border. As in the splenic infarcts, no evidence of an infectious process was present. Hematoxylin and eosin stain, original magnification × 100.

FIG. 8. Every area of the lungs had this general appearance. Numerous macrophages (*upper*) are present in air spaces. Alveolar walls appear cellular and thickened, and alveolar lining cells are prominent. Fibrin exudation has occurred into air spaces, especially the larger ones, as seen at lower right. Hematoxylin and eosin stain, original magnification × 100.

of various organs, produced much of the clinical symptomatology, and led to the patient's death.

Final anatomic diagnoses: Acute bacterial endocarditis (staphylococcal) with destruction of the lateral portion of the mitral valve and superimposed organizing thrombus; organizing abscesses of the left frontal lobe of the brain and in the retroperitoneal space near the aortic bifurcation; organizing and recent infarcts of the spleen and kidneys, extensive, and multiple small infarcts of the myocardium, all due to thromboemboli; organizing mural thrombus in the right atrium; hyperplasia of the lymph nodes generally, moderate, and of the spleen (480 gm.) marked; cardiac dilatation and hypertrophy (450 gm.); hydrothorax: right, 600 ml.; left, 400 ml.; organizing fibrinous pneumonia, widespread, consistent with that seen in uremia; multiple fibrous adhesions of the pleural and peritoneal surfaces.

DISCUSSION

DR. REINHARD: I presume that the fairly extensive thrombi present in organs all over the

body is a reflection of the profound cardiac failure with resultant sluggish blood flow. Was there anything to suggest a toxic effect on the vessel walls secondary to the infection?

DR. O'NEAL: I do not know; but I certainly did think that the terminal problem was principally one of thrombosis and thromboembolism, rather than infection.

DR. REINHARD: Have you any comment, Dr. Harford, about the effect of chemotherapy on the progress of the lesions here? It would appear that the chemotherapy was partially effective in view of the duration of the staphylococcal infection. After all, the patient had been in the hospital several months, and there were surprisingly few abscesses. Were you impressed with that?

DR. HARFORD: Yes, I was. I should like to say, also, that whenever a patient has staphylococcal bacteremia, one wonders where in the body the bacteria have become lodged and what unrecognized lesions they may be causing. In this case, an abscess of the brain occurred.

Case Reports

Lipoid Dermato-Arthritis and Arthritis Mutilans*

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LIPOID dermato-arthritis is the name given by Warin et al. [*1*] to a rare disease involving skin, synovial membranes and bone. Histologically, one finds collections of irregular, multinucleate, foam-free giant cells, together with numerous histiocytes and inflammatory cells in the skin and often in the synovia. The disease is distinguished clinically by the association of multiple papular and nodular skin lesions with a polyarthritis that in many respects mimics rheumatoid arthritis. Roentgenographic and laboratory features, although not of themselves unique to this condition, have been of aid in the differentiation from closely allied disorders. Roentgenograms of involved joints have for the most part revealed changes indistinguishable from rheumatoid arthritis but in four of the previously reported cases [*1–4*] and the case report to follow the osseous involvement was very striking, bone destruction and resorption occurring to a degree seldom recorded in the literature on arthritis. No consistent abnormalities have been reported in the blood lipid patterns. Serum calcium and phosphorus levels have been normal. The erythrocyte sedimentation rate has been surprisingly low in the reported cases.

Targett [*5*] in 1897 probably was the first to describe this illness when he described a sixty-five year old woman of "rheumatic and gouty habit" who had nodular skin lesions. The characteristic irregular polynucleated giant cells were found histologically but because a description of the joint involvement was not included in the report we have arbitrarily chosen not to include this case in the series to be reviewed. Weber and Freudenthal [*6*] in 1937 were the first adequately to describe the entity. Their patient was a thirty-five year old man with subjective and objective evidence of polyarthritis and tenosynovitis associated with cutaneous nodules. On microscopic examination the lesions were typical of lipoid dermato-arthritis and thus we believe that the authors were mistaken when they considered the malady to be one of the xanthomatous disorders. The absence of foam cells and only faint staining with Sudan III is certainly against a diagnosis of xanthoma. Portugal et al. [*7*] in 1944 described the second case under the name of "generalized giant cell histiocytomatosis." Allington [*8*] in 1950 reported the case of a sixty-three year old woman with the classic clinical and histologic features of lipoid dermato-arthritis although at that time the suggested diagnoses included myoblastoma, ganglioneuroma and histiocytoma. It was not until after Caro and Senear [*9*] reported two additional cases in 1952 that it was recognized that all three patients shared a common disease. These authors suggested the name reticulohistiocytoma and they were the first to demonstrate the specific histologic lesion in the synovia. Following Caro's presentation, Montgomery [*10*] added the sixth case. This was a twenty-four year old woman who was the first of the series to have extremely destructive joint lesions eventuating in the syndrome of arthritis mutilans to be discussed later. Evans [*11*] in 1952 and then Warin [*3*] at the same 10th International Congress of Dermatology added the seventh and eighth cases. Warin's patient was a fifty-one year old woman whose arthritis was characterized by marked resorption of bone, producing the "opera glass" or "concertina" deformity of the hands. Typical giant cells were found in the skin, synovia, bronchial nodes and

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endocardium. Goltz and Laymon [*12*] added two cases in 1954 under the name of "multicentric reticulohistiocytosis of the skin and synovia." These authors suggested that the previously reported cases could be separated into two groups: One group demonstrated the complete syndrome of the typical skin lesions associated with a definite arthritis; the other a doubtful, atypical or incomplete group in which arthritis was lacking. Kierland [*13*] in 1955 added another classic case, as did Davies and Wood [*14*] in the same year. Johnson and Tilden [*4*] reported the thirteenth case and named the syndrome "reticulohistiocytic granuloma." Theirs was the third such patient to have arthritis mutilans. Warin et al. [*1*] reported two more cases in 1957; one of these became the fourth to progress to a mutilating form of arthritis. These authors suggested the name "lipoid dermato-arthritis" for the entity, to eliminate the neoplastic implications of the term "reticulohistiocytoma." Lapiere et al. [*15*] added a case in 1957, and Lyell and Carr [*16*] in 1958 reported the seventeenth and most recent case.

CASE REPORT

J. D., a thirty-six year old woman, was admitted to the University of Michigan Medical Center on May 13, 1958, with complaints of generalized body pain, most severe in the hips, knees, ankles and feet. She had been unable to walk for four years prior to admission because of arthritis. Two years prior to admission she had the onset of weakness, urinary frequency, nocturia and polydypsia.

Past history revealed a normal birth and early development except for small stature similar to that of her mother. She had had a spontaneous abortion at the age of twenty-one and the following year delivered a premature infant that survived only minutes. The next year she was again pregnant and this terminated with a stillbirth at eight months. Albuminuria and a pelvic infection were discovered shortly thereafter and a total hysterectomy was performed. She was told of hypertension while in her teens, and at age twenty-four, because of severe headaches, she underwent a bilateral splanchnicectomy at another hospital.

The present illness began at age twenty-nine with the onset of pruritic skin lesions. The consulting dermatologist* described the condition as follows: "The illness began six months ago as a diffuse redness over the arms and face. While under treatment elsewhere, itching papules developed over the arms, hands, face and neck which persisted in spite of treatment. Patient also complained of nervousness and painful joints." Examination then revealed a papular eruption over the dorsum of the hands, arms, face, V area of neck, and in and about the nares and the ears. The lesions were firm, yellowish papules concentrated about the finger joints and paronychial areas. They varied in size from 2 mm. to pea-sized; the larger ones were about the elbows. The urine was free of sugar. Bone roentgenograms were said to be within normal limits at this time. A biopsy specimen of one of the skin nodules was obtained. About this time she was told of thyroid trouble and was given 2 gr. of thyroid daily along with a weight reduction diet. A 77 pound weight loss occurred over the next year.

In 1952, at age thirty, severe pain, heat, swelling, redness and stiffness in both knees developed. Within several weeks there was similar involvement of the ankles and hips. After one year the shoulders, elbows, wrists and fingers were all actively involved. The patient has been non-ambulatory since 1954 due to the severity of the arthritis, especially in the hip joints. She also became aware at this time of shrinking and hypermobility of her fingers. Simultaneously, there was a lessening of pain in the digits. The skin nodules cleared spontaneously except for a few which persisted over the face.

Physical examination revealed a short, obese, white woman, uncomfortable, unhappy and appearing older than her stated age. The blood pressure was 140/98 mm. Hg (right arm, sitting), the pulse 88 and regular. Significant physical findings were confined to the skin and musculoskeletal systems. A number of small yellowish brown nodules, the largest 5 mm. in diameter, were present over the lateral borders of her nose. Xanthelasmas were present on both upper eyelids. (Fig. 1.) An acute, macerated dermatitis was present over the vulvar area and on the inner thighs, typical of candidiasis. The shoulders were painful and motion restricted, abduction being limited to 45 degrees bilaterally. There was slight swelling, warmth and moderate limitation of motion of the elbows. The dorsal tendon sheaths of the wrists were easily palpable, with slight thickening of the joint capsule and only minimal loss of motion. There was marked shortening of the fingers, which varied from 1 to 1½ inches in length, associated with telescoping of the soft tissues and a marked hypermobility. (Fig. 2.) There was no evidence of active inflammation of the joints and the fingers were painless on motion. The patient would permit only minimal movement of her hips, due to pain, and kept these joints at 10 degrees flexion. There was some swelling and tenderness of the knees with pain on motion. The ankles were painful, tender and slightly swollen but with near normal range of motion. The right fifth toe had a telescoping deformity similar to the fingers. No rheumatoid nodules were noted.

Laboratory findings included a hemoglobin of 12.4 gm. per cent, hematocrit 45 per cent and a sedimentation rate of 30 mm. per hour (Wintrobe). The white blood count was 8,000 per cu. mm. with a normal differential. Examination of the urine revealed it to be acid, specific gravity of 1.026, no albumin, 2-plus glycosuria, 2-plus acetonuria and numerous white blood cells.

* Dr. Frank Stiles, Lansing, Michigan.

Results of the serum Kahn test, two L.E. cell preparations, the Ziff sheep cell hemagglutination test, the Singer and Plotz latex fixation test and the bentonite flocculation test of Bozicevich, Bunim et al. were all negative. The results of the following tests were all within normal limits: ASL-O titer, C-reactive protein, serum proteins, blood urea nitrogen, serum electrolytes, calcium, phosphorus, alkaline phosphatase, thymol turbidity, bilirubin, prothrombin concentration and bromsulfalein retention. A twenty-four-hour urine collection was negative for 5 hydroxyindoleacetic acid. Two twenty-four-hour urine specimens obtained while on a regular diet contained 31 and 29 mg. of calcium.

The protein-bound iodine was 6 gamma per cent, the twenty-four-hour I^{131} uptake was 27.8 per cent, serum cholesterol was 220 mg. per cent with 69 per cent esters, phospholipids were 165 mg. per cent and total lipids were 700 mg. per cent. An electrocardiogram revealed left axis deviation but was otherwise within normal limits. The initial fasting blood sugar was 275 mg. per cent. A cephalin flocculation test was 2 plus and 4 plus at twenty-four and forty-eight hours, the gamma globulin was 14.3 units, and paper electrophoresis of the serum proteins showed an albumin of 41 per cent, alpha one globulin 4.2 per cent, alpha two globulin 12 per cent, beta globulin 15 per cent and gamma globulin 28 per cent.

A chest roentgenogram did not reveal any significant cardiopulmonary abnormalities. There was extensive destruction of the heads of the humeri bilaterally, with maintenance of the joint space. There was also destruction of the distal portions of the clavicles. Roentgenograms of the skull did not reveal any abnormalities. Roentgenograms of the knees demonstrated extensive subcortical destruction of the articular surfaces bilaterally, with maintenance of the joint spaces. There was no periarticular osteoporosis. The same process involved the patellae. Films of the feet and ankles showed marked subcortical destruction of the articular surfaces of the tarsal bones, again with joint space preservation. There was complete dissolution of the diaphysis of the fourth and fifth proximal phalanges on the left and the fourth phalanx on the right. Bilateral acetabular protrusions encroaching upon the pelvic space were evident on the films of the pelvis. (Fig. 3.) There was complete destruction of the femoral heads and femoral necks, and articulation of the distal femoral neck and greater trochanter with the superior acetabular rim bilaterally. Roentgenograms of the elbows showed almost complete destruction of the distal humeral condyles bilaterally, with absorption of the proximal radial heads and increased size of the ulnar fossae bilaterally. Joint spaces were maintained. (Fig. 4.) Films of the hands revealed the most extensive destruction, especially the articular, subcortical destruction of the carpal bones. The metacarpals were least involved. There was almost complete dissolution of the middle phalanges of all the fingers; the distal tufts of the terminal phalanges remained. (Fig. 5.) Films of the dorsalumbar spine showed only minimal

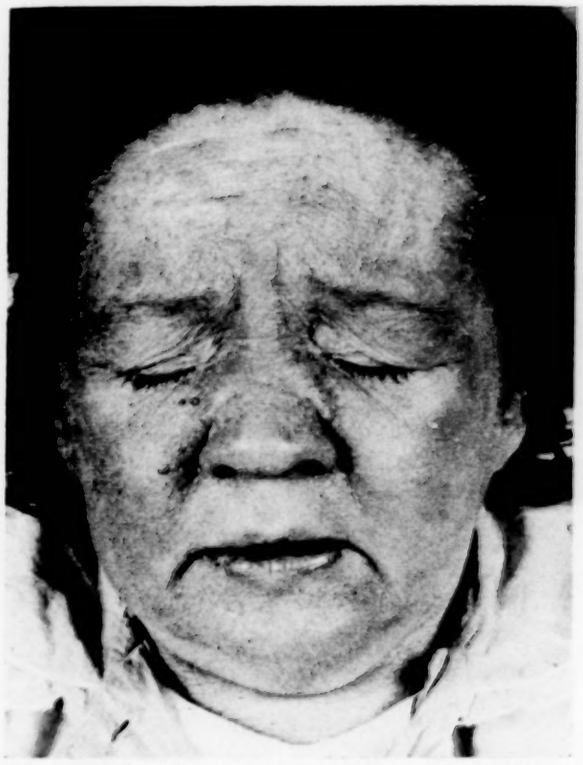

FIG. 1. J. D. (May 1958). Xanthelasma at the inner canthi, with specific nodular lesions along borders of the nose. Diffuse erythema and scaliness due to incidental contact dermatitis.

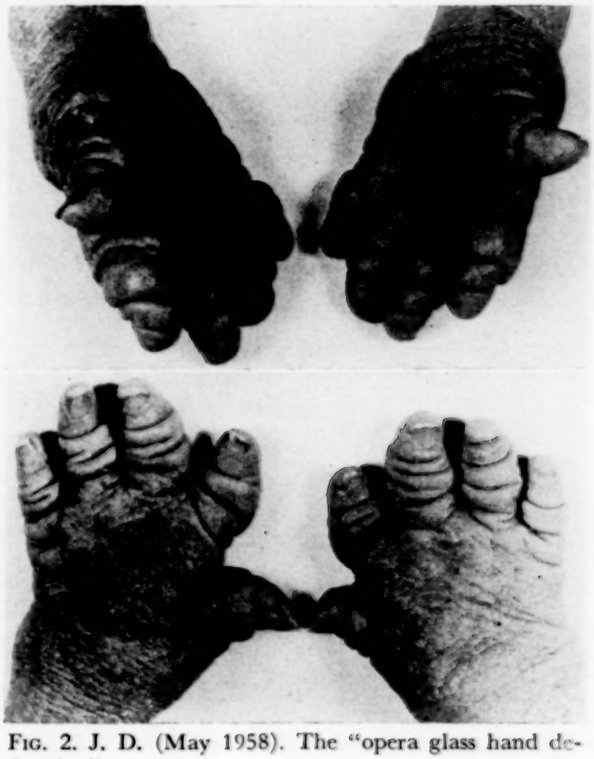

FIG. 2. J. D. (May 1958). The "opera glass hand deformity."

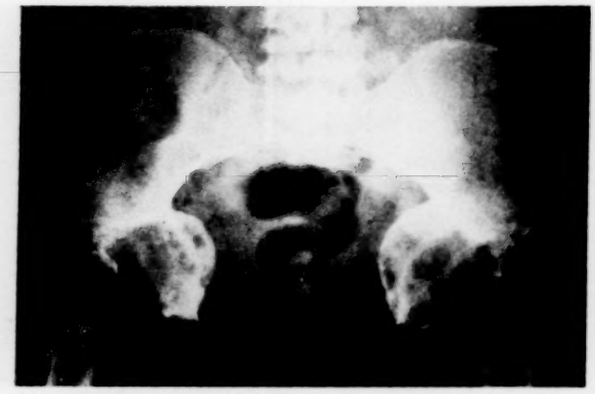

FIG. 3. Anteroposterior roentgenogram of the pelvis showing destruction of femoral heads and acetabular protrusions (protrusio acetabuli or Otto pelvis).

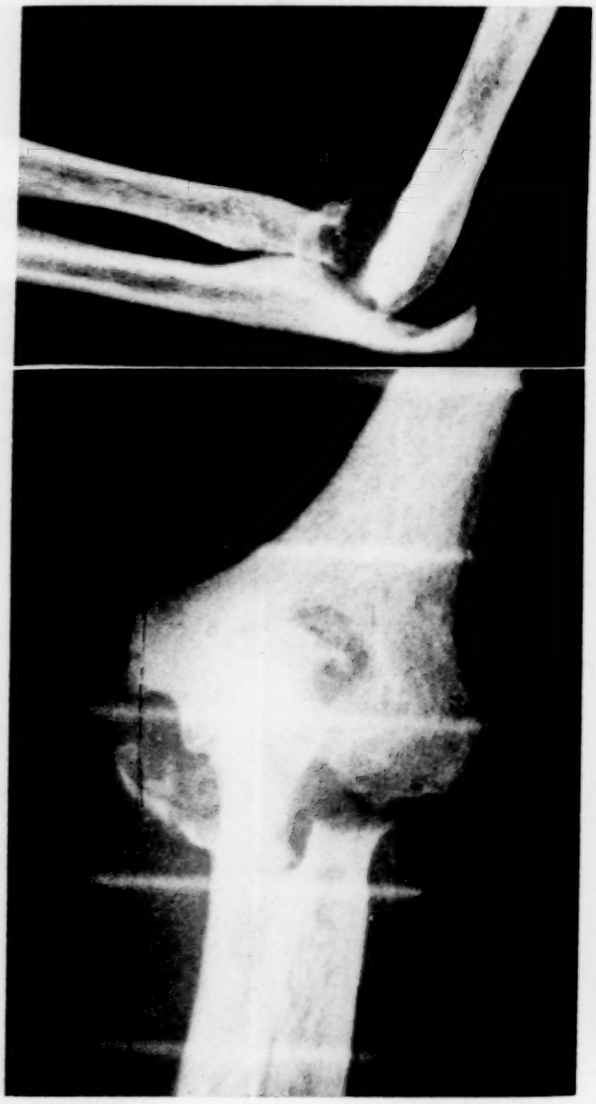

FIG. 4. Lateral and anteroposterior roentgenograms of the elbow showing destruction of the humeral condyles and absorption of the radial head.

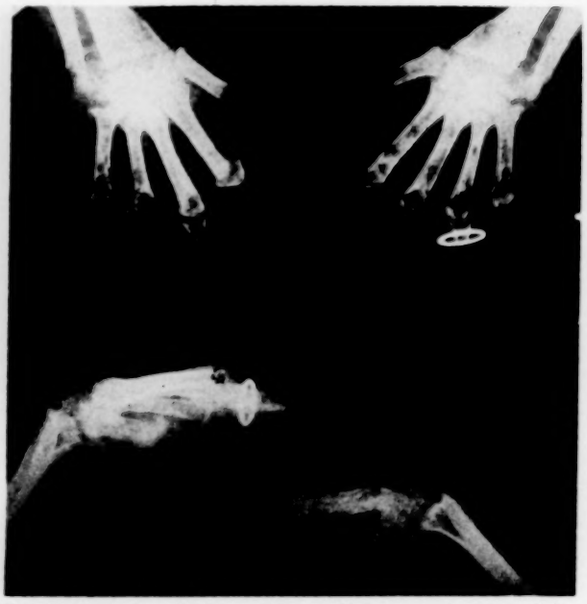

FIG. 5. Anteroposterior and lateral roentgenograms of the hands showing destruction of the carpal bones and almost complete dissolution of the middle phalanges.

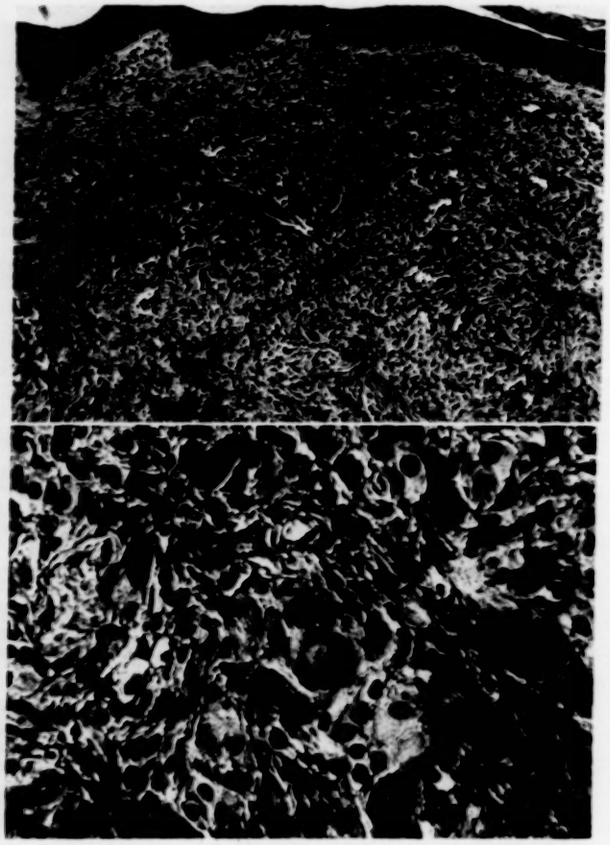

FIG. 6. Biopsy specimen of skin nodule (1951). Intradermal collections of histiocytic cells. Binucleate and multinucleate cells are present. Infiltrate of small round cells in the adjacent dermis. Hematoxylin and eosin stain, original magnification × 75 and 300, respectively.

degenerative changes. Films of the cervical spine revealed basilar invagination with possible assimilation of the first cervical spine with the occipital structure of the skull.

While in the hospital an attempt was made to control the patient's diabetes with diet and tolbutamide. This did not result in satisfactory control and insulin was substituted for tolbutamide, with good results. Conservative measures, including the administration of salicylates to tolerance and physical therapy, afforded moderate relief of her joint symptoms.

A synovial needle biopsy of the left knee was performed twenty-four hours after the intravenous injection of 60 mg. of saccharated iron. Subsequently a punch biopsy was performed on one of the nodular lesions of the face. The iron was given in an attempt to determine if the cells involved in the specific lesion were histiocytic from a functional viewpoint. The microscopic descriptions of the specimens are as follows:

Biopsy of skin nodule (1951) (Fig. 6): Within the dermis there was a circumscribed but non-encapsulated tumor consisting of a pure culture of histiocytic cells. It was separated from a thin but intact epidermis by a narrow zone of collagenous tissue. The histiocytic cells were of varying size and shape with slightly vesicular nuclei and abundant pale sometimes granular cytoplasm. Binucleated and multinucleated cells were present, the latter being of foreign body type with small hyperchromatic nuclei. No Touton giant cells were present. The presence of scattered division figures suggested an actively proliferating lesion but other cytologic features of a malignant neoplasm were absent. Bundles of mature collagen of dermis persisted throughout the involved area. There were perivascular collections of lymphocytes and small mononuclear cells in the adjacent dermis but only occasional lymphocytes and no eosinophils within the lesion. There was no fibroblastic reaction. *Diagnosis:* Reticulohistiocytosis (reticulohistiocytoma or reticulohistiocytic granuloma) of skin.

Synovial biopsy (1958): There was a small amount of synovial mesothelium in this specimen; most of the material was edematous connective tissue. The mesothelial cells were prominent but could not be considered hyperplastic. A few small mononuclear cells, mainly lymphocytes, were present but there were no large histiocytic cells such as those observed in the lesion of skin. Iron stains on this tissue were negative.

Biopsy of nodule on side of nose (1958): Within the upper dermis but separated from the epidermis by a thin zone of collagenous tissue were groups of pale histiocytic cells. The overlying epidermis was flattened with loss of rete pegs. There was no significant number of inflammatory cells intermixed with the histiocytes but small mononuclear cells and lymphocytes were about blood vessels in the adjacent dermis. Many of the histiocytic cells were less well defined than in the previous lesion and had a spindled appearance resembling fibroblasts. A few multinucleated giant cells were present. Several histiocytes contained phagocytized material. Iron stains revealed no stainable material within histiocytic cells. No metachromatic granules were visible in the histiocytic cells but their cytoplasm was faintly positive with a periodic acid-Schiff stain. *Diagnosis:* Reticulohistiocytosis of skin.

The skin lesions described in 1958 were very similar to those of 1951 but smaller and less well defined. Division figures were less frequent and spindled forms of histiocytes more prominent. These features suggest that this lesion may be regressing.

This patient has now been followed up at University Hospital for twenty-two months. There has been a slow but definite improvement in her ambulation. There has been no apparent progression in symptoms or signs. Results of repeated latex-fixation tests for the rheumatoid factor have been negative. Roentgenograms of the chest, clavicles, hands and feet were repeated eighteen months after the initial hospitalization here. There were no definite changes noticeable on these films in the interim.

COMMENTS

Our patient illustrates the typical features of the severe form of this disorder. Including J. D., thirteen of the eighteen acceptable cases have occurred in women. The age of onset has varied from twenty-four to sixty-three years, eleven having occurred between the ages of forty and fifty-four. In J. D. the illness began at age thirty and, like the other members of the series with an early age of onset, her course has been one of marked osseous destruction and incapacitation. Her initial manifestation was the skin lesions; the polyarthritis followed by several months. In the series under review, six cases began with arthritis, five with the skin lesions and in six there was essentially a simultaneous onset of both skin and joint manifestations. The skin lesions have been strikingly similar in appearance and location throughout the series. Each report, with one exception, has stressed the occurrence of nodules about the fingers—especially the periarticular and periungual areas of the dorsal surface of the digits. Only Warin's third patient [*1*] (No. 15 in Table 1) was not mentioned as having the lesions on her fingers. Other areas of special predilection, in approximate order of frequency, include the dorsum of the hands, the face, ears, forearms and V area of the neck. The lesions are usually colorless and in the same patient may vary in size from miliary or minute superficial nodules to several centimeters in diameter. They may be pruritic, tender or even painful, and are prone

TABLE I

PERTINENT FEATURES OF REPORTED CASES OF LIPOID DERMATO-ARTHRITIS

Case No.	Authors	Age at Onset (yr.)	Sex	Arthritis Mutilans	Tenosynovitis of Wrists	Xanthelasma	Location of Skin Lesions	Thyroid Disease	Cholesterol (mg. %)	Serum Lipids	Blood Glucose	Sedimentation Rate
1	Weber, Freudenthal [6]	35	M	No	Yes	—	Fingers, hands, forearms, face, ears, nose, back	—	110–350	—	Normal	—
2	Portugal et al. [7]	43	M	No	Yes	—	Fingers, hands, ears, extremities	—	—	—	—	—
3	Allington [8]	63	F	No	Yes	—	Fingers, hands, forearms, nose	Toxic adenoma	180	—	—	—
4	Caro, Senear [9]	42	M	No	Yes	—	Hands, ears, scalp, face, fingers, nose	—	145	—	—	7
5	Caro, Senear [9]	34	F	No	—	—	Fingers, face, ears, arms, V-neck	Graves' disease	190	—	Normal	9
6	Montgomery [2,10]	24	F	Yes	—	Yes	Fingers, face, lips, generalized	—	137	Normal	—	19, 15
7	Evans [11]	52	F	No	Yes	Yes	Face, lips, generalized	—	130–250	—	Normal	—
8	Warin et al. [1,3]	49	F	Yes	Yes	Yes	Fingers, face, lips, tongue, generalized	—	125–180	—	Normal	5, 41
9	Goltz, Layman [12]	40	F	No	—	—	Face, scalp, chest, neck, fingers	Graves' disease	—	—	Normal	80, 33
10	Goltz, Layman [12]	52	M	No	Yes	—	Fingers, ears	—	—	—	—	—
11	Kierland [13]	54	F	Early	—	Yes	Hands, fingers	Graves' disease	150, 143 234, 343	Normal	—	—
12	Davies, Wood [14]	47	F	No	—	—	Fingers, face, neck, ears	—	Normal	—	—	Norma
13	Johnson, Tilden [4]	26	F	Yes	—	—	Face, fingers, arms, abdomen, back, legs	—	500, 525 350, 160	—	—	—
14	Warin et al. [1]	48	F	No	—	—	Hands, fingers, face, mouth, tongue, generalized	—	—	—	—	—
15	Warin et al. [1]	25	F	Yes	—	—	Face, arms, generalized (hands not mentioned)	—	98–190	—	—	Normal
16	Lapiere [15]	50	M	No	—	Yes	Hands, fingers, face, neck, generalized	—	Normal	Normal	—	76
17	Lyell, Carr [16]	52	F	No	Yes	Yes	Fingers, ears, nose	—	225–275	—	—	2, 15

NOTE: — = not reported.

to wax and wane. Complete or nearly complete clearing has been the eventual outcome in many of the reported cases.

The arthritis, which we consider an essential component of the syndrome, resembles rheumatoid arthritis in the majority of cases. Involvement tends to be multiple and symmetrical; the smaller joints are especially prone; pain, tenderness and stiffness with synovial thickening are the common findings; and, although remissions may occur, the usual course leads to chronic disability in the majority. Although J. D. was not under our observation during the more active stages of her disease, we believe that her illness would fulfill the diagnostic criteria [*17*] for "definite rheumatoid arthritis." Yet there are major differences, including the specific histologic picture of lipoid dermato-arthritis, the frequent finding of a low erythrocyte sedimentation rate in the face of active arthritis, and in our patient, at least, the negative reaction to serologic tests for the rheumatoid factor. Vaughn [*18*] and other investigators [*19,20*] have emphasized the increased incidence of positive reactions to agglutination tests for the factor in patients with the more advanced joint disease due to rheumatoid arthritis. Our patient is the fifth of the eighteen reported cases of lipoid dermato-arthritis to show the changes of arthritis mutilans. Smyth [*21*], after reviewing the literature of rheumatoid arthritis, described the occurrence of bone resorption of comparable degree but the incidence was considerably less than that found in the series reviewed here. Preservation of the joint spaces and relatively minimal periarticular osteoporosis, as described on the roentgenograms of J. D., also serves to differentiate the illness from rheumatoid arthritis.

Table 1 indicates other rather consistent features of lipoid dermato-arthritis. Xanthelasma was striking in our patient and was specifically mentioned in six others of the series. Yet serum cholesterol levels have tended to be in the normal range throughout the series. The serum lipid levels were also normal in the four patients in whom determinations were reported. Tenosynovitis presenting as soft fluctuant swellings or ganglia at the dorsum of the wrists was mentioned in 50 per cent of the cases. A diagnosis of hyperthyroidism was made in four of the reported cases but this seems likely to be an incidental finding having no predictable effect on the course of the disease. Our patient was once suspected of being hypothyroid but appeared euthyroid under our observation. She is the first of the group to be a proved diabetic. This, too, probably represents coincidental disease but a particularly unfortunate one that has added to the morbidity of our patient. Self administration of insulin was clearly impossible, hence a trial of oral therapy with tolbutamide was attempted. As one might anticipate with the ketogenic type of diabetes, the trial was unsuccessful and she has required insulin therapy. A search for other endocrine abnormalities was negative.

Arthritis Mutilans. This term was given by Stursberg [*22*] in 1935 to the polyarthritis seen in two patients that was characterized by marked destructive changes in the joints. Actually it was Marie and Leri [*23*] in 1913 who reported the first such case in which the destructive and resorptive processes in the bones and joints of the fingers were so marked that there was telescoping of one bone upon the next. These authors termed the condition "la main en lorgnette." Subsequently, similar cases have been reported under the name of "the opera glass hand deformity" [*24–26*]. Weigeldt [*27*] described an unusual tapering of the distal ulna forming a pencil-like deformity associated with the opera glass hand deformity. Otto [*28,29*] in 1824 described the results of massive bone resorption in the hips leading to absorption of the head of the femur and mesial displacement of the inner wall of the acetabulum. This affliction has been referred to as the Otto pelvis or protrusio acetabuli and is another manifestation of the mutilating course chronic arthritis can pursue. It is said to occur in 5 per cent of cases with rheumatoid hip involvement. Our patient exhibited all these changes of arthritis mutilans as well as similar resorptive changes in multiple other joints. Severe resorptive changes have been described in arthritis due to a variety of etiologies. Thus lipoid dermato-arthritis must be added to psoriatic arthritis, rheumatoid arthritis, scleroderma, porphyria and thromboangiitis obliterans as a cause of arthritis mutilans.

Histology. Zak [*30*] was the first to describe the histology of reticulohistiocytoma. In his four cases the skin lesions were not associated with arthritis and hence are not included in this series as examples of lipoid dermato-arthritis. Subsequent reports of the pathologic condition of this disease have been very uniform. It is the large bizarre-shaped, multinucleated giant cell

which forms subepidermal aggregates that is the specific pathologic lesion. These giant cells can contain from 2 to 20 nuclei and have homogenous (but not foamy) cytoplasm with little or no demonstrable lipid. The cells are usually imbedded in a dense fibrous stroma. Specific staining characteristics of these cells aid in their identification. Thionine blue stain does not elicit the presence of Nissl granules, thus differentiating this entity histologically from ganglioneuroma. Sudan III stains do not give the brilliant uptake characteristic of the foam cells of xanthomatous disorders but rather there often is only a fine pinkish hue or minute droplets in the cytoplasm. This staining quality also helps to differentiate this disease from myoblastoma. Prussian blue reactions indicate the lesions to be rich in iron content [*16*] but the giant cells themselves seem to contain little or no iron. Caro and Senear [*9*] believe that the demonstration of colloidal iron uptake by the giant cells with vital staining technics proves the reticuloendothelial nature of the cells. The multinucleate giant cells are periodic acid-Schiff positive according to several authors [*1,2,15*]. Lyell and Carr [*16*] give an excellent review of the staining characteristics of the lesions and their probable significance. They conclude that the giant cells contain a glycolipid. Beside the giant cells, there are, in varying amounts, mononuclear cells. These include histiocytes with large pale irregular nuclei, lymphocytes and plasma cells. Davis and Wood [*14*] believe that there are histologic differences between the solitary skin lesions and the lesions found in the complete syndrome.

DIFFERENTIAL DIAGNOSIS

The place of lipoid dermato-arthritis in the spectrum of joint diseases is hard to define. Certainly the arthritic manifestations of this syndrome are compatible with severe rheumatoid arthritis, and, as already mentioned, even the multilating forms are found in both diseases. Yet the associated skin lesions, with their characteristic appearance, location and histology, together with a similar pathologic process demonstrable in the synovia of several of the patients reported on, warrant consideration of this syndrome as a specific entity. The negative reaction to serologic tests for the rheumatoid factor in our patient support this concept.

There have been several closely allied cases in the literature which we have not included in this series because of differentiating features. Graham and Stansfeld [*31*] in 1946 told of a twenty year old man with polyarthritis simulating rheumatoid arthritis and the presence of nodular cutaneous lesions grossly resembling those of lipoid dermato-arthritis. However, on microscopic study the lesions proved to be quite different. Multinucleated giant cells were absent and the predominate cell was mononuclear with a "foamy" cytoplasm. The authors concluded that these were xanthoma cells. This case is of special interest for it suggests a linkage between the xanthomatous disorders and lipoid dermato-arthritis. Interestingly, the foamy "xanthoma cells" did not take up lipid stains in droplet manner, behaving much like the cells of lipoid dermato-arthritis. Fletcher [*32*] in 1946 described a forty-two year old man with progressive polyarthritis in whom numerous subcutaneous nodules developed subsequently. This case was distinguished by marked osseous disease due to a granulomatous process. Histologically, it could be separated from the disease under discussion by the presence of typical foam cells that gave a positive stain for cholesterol and fine orange-red droplets appeared after sudan staining. In addition, many multinucleated giant cells of the foreign body type were seen. Necrobiosis was a prominent feature, thus differing in another respect from lipoid dermato-arthritis. Golden and Richards [*33*] reported two cases of polyarthritis accompanied by xanthogranulomatous lesions in adjacent bones and soft tissue. In one of the cases there were large bursal cysts adherent to the skin and in communication with joint spaces. The cysts and bony lesions were made up of multinucleated giant cells and sheets of "foamy" or "xanthoma" cells. Sudan black staining revealed many fine droplets in the xanthoma cells and more coarse droplets in the giant cells. One of the patients had hypercholesterolemia. The authors considered that their cases bore a strong resemblance histologically to the third or xanthomatous phase of Hand-Schüller-Christian disease, so called histiocytosis X. Thannhauser [*34*] in his excellent book on the lipoidoses characterizes lipoid dermato-arthritis and expresses the opinion it is unrelated clinically or histologically to the generalized form of eosinophilic xanthomatous granuloma (histiocytosis X, acute reticuloendotheliosis, generalized form of Schüller-Christian disease).

SUMMARY

The eighteenth case of lipoid dermato-arthritis is presented, and the world literature pertaining to this and closely allied conditions is reviewed.

The reasons for believing lipoid dermato-arthritis to be a specific disease entity are discussed. The association of skin lesions of typical morphology, histology and location with a polyarthritis in which, in some of the cases at least, the synovia exhibit a pathologic process similar to that in the skin lesions make this a readily recognizable disease. Other salient features include the high incidence of xanthelasma in essentially normocholesterolemic persons and the frequency with which tenosynovitis occurs. Additional manifestations include those of "arthritis mutilans"—the opera glass hand, protrusio acetabuli and pencil-like tapering deformities of the ulnae and clavicles.

Reactions to serologic tests for the rheumatoid factor were negative on multiple occasions in the case described. In view of the advanced joint disease, this is considered further evidence that the disease under discussion does not represent the fortuitous association of rheumatoid arthritis with unusual skin lesions but is a specific entity.

ADDENDUM

Since this manuscript was submitted, a report by Albert et al. [*35*] has come to our attention. These authors described a fifty-five year old Negro woman with the clinical and histologic features of lipoid dermato-arthritis. This patient also showed marked destructive changes in her joints. Interestingly, this patient had a negative reaction to the latex test for rheumatoid arthritis and moderate elevations of the total blood lipids and cholesterol.

Acknowledgment: We express our gratitude to Dr. Murray R. Abell, Professor of Pathology, University of Michigan, for reviewing the histological sections; to Dr. William D. Robinson, Professor and Chairman of the Department of Internal Medicine, University of Michigan, for his helpful criticisms and suggestions; and to Mrs. Dorothy Rickard for technical assistance. The slide for Figure 6 was supplied by Dr. Herman K. Pinkus, Monroe, Michigan.

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Myocardial Infarction in a Fifteen Year Old Boy*

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In the past fifteen years several reports have emphasized the occurrence of atherosclerotic heart disease in young adults. Other causes of coronary artery disease occurring in children have been described. It is evident that myocardial infarction is not restricted to the elderly or even to the adult patient.

We recently observed a fifteen year old boy who survived a myocardial infarction. His age tended to exclude several of the etiologies of coronary disease found in childhood; yet he was younger than most of the patients with atherosclerotic heart disease described in the literature. This case is of additional interest because coronary arteriography provided an anatomic demonstration of severe, localized coronary arterial narrowing.

CASE REPORT

This fifteen year old white boy (born August 22, 1945) was admitted to the University of Oregon Medical School Hospital (UOMS No. 26-18-45) for the first time on December 28, 1958. He had been well until the preceding September when, after running a 220 yard dash, he became inordinately dyspneic, weak, and thereafter collapsed. Within five minutes he began to feel better; all symptoms soon disappeared. No chest pain was experienced. A physician who was consulted found a heart murmur and electrocardiographic abnormalities. During the three-month interval until admission to our hospital the patient had been well.

No one in his family was known to have had heart disease at an early age and there was no family history of hypertension or diabetes mellitus. His father was well at age forty-two. His mother died at twenty-nine years of age during a postpartum depressive reaction. Three siblings were apparently healthy.

The patient was a tall, slender boy who felt well. The peripheral pulse was 80 per minute and of normal character, respirations were 16 per minute and the blood pressure was 120/60 mm. Hg. His height was 73 inches; his weight 152 pounds. The optic fundi were normal. The heart was not enlarged and no ventricular overactivity or thrill was present. The cardiac rhythm was regular. A soft, ejection systolic murmur was heard along the left sternal border and became softer with inspiration. Normal inspiratory splitting of the second sounds was present. The remainder of the examination was within normal limits.

The hemogram, erythrocyte sedimentation rate and urinalysis were all within normal limits. A fasting blood glucose was 102 mg. per cent. Blood lipid measurements were total serum lipids, 398 mg. per cent; phospholipids, 195 mg. per cent; cholesterol, 119 mg. per cent, with 70 per cent esters; neutral fats and fatty acids, 84 mg. per cent. Chest roentgenograms and cardiac fluoroscopy showed a normal cardiac silhouette and pulmonary vascular shadows.

An electrocardiogram displayed deep Q waves in leads I, AVL, and V_4 through V_6. (Fig. 1.) The R:S ratio was greater than one in lead V_1 with an R wave of 15 mm. T wave abnormalities were present. The tracing was consistent with a lateral myocardial infarction with posterior involvement.

A spatial vectorcardiogram was obtained, using the cube system of electrode placement [*1*]. (Fig. 2.) In the horizontal projection, there was large initial anterior and rightward movement of the QRS loop, with the result that most of the loop was located anterior to the isoelectric spot. The QRS loop in the frontal projection was oriented vertically, with counterclockwise inscription. The records indicated a posterolateral infarction.

The results of right heart catheterization were entirely normal, with no evidence of a left-to-right shunt, pulmonary hypertension or pulmonary valve gradient. The configuration of the right ventricular pressure curves was normal. Selective angiograms of the outflow tract of the right ventricle and pulmonary artery did not demonstrate any abnormalities.

* From the Division of Cardiology, Department of Medicine, and the Department of Radiology of the University of Oregon Medical School, Portland, Oregon. This study was aided by grants from the U. S. Public Health Service H-3275 (CI), the Oregon Heart Association and the Mallinckrodt Chemical Works.

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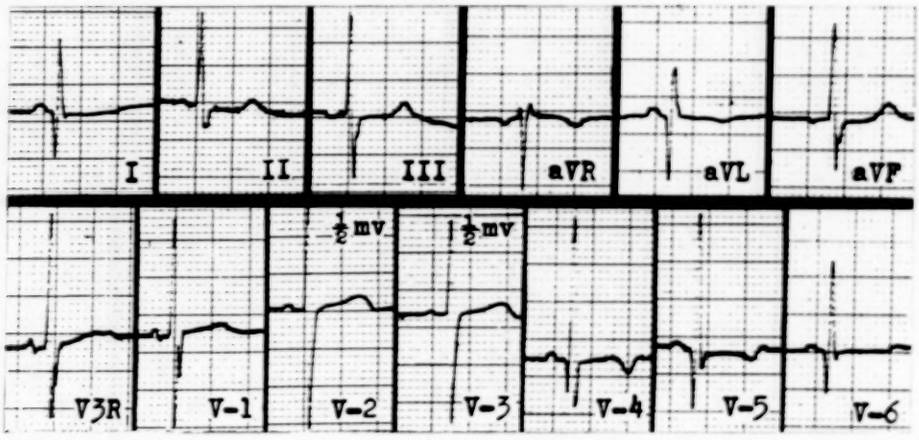

FIG. 1. The electrocardiogram displays deep Q waves in leads I, AVL, and V_4 through V_6. The R:S ratio exceeds one in lead V_1, and T wave abnormalities are present. The tracing is compatible with lateral and posterior infarction.

The patient was discharged from the hospital following these examinations and was seen periodically as an outpatient. No symptoms occurred. The previously recorded electrocardiographic abnormalities persisted.

He was readmitted to the hospital for further evaluation on August 10, 1959. Left ventricular and proximal aortic angiography were performed by percutaneous retrograde catheterization from the femoral artery [2]. A left ventricular injection of contrast agent (30 cc. ditriokon) showed no abnormalities of the aortic valve or proximal aorta. A second injection was made with the catheter tip just above the aortic valve, while the patient performed a Valsalva maneuver. Good filling of the coronary arteries was obtained and the findings were striking. (Fig. 3.) Just distal to the bifurcation of the left coronary artery, marked narrowing was present in both the anterior descending and circumflex branches. These vessels were tiny throughout their distribution. The entire anterior and lateral portions of the left ventricle appeared to have a markedly reduced blood supply. The coronary ostia were of normal size. The right coronary artery was large, with one branch extending almost to the cardiac apex.

It was concluded that the patient had sustained a large lateral myocardial infarction due to marked narrowing of the branches of the left coronary artery. He has continued to be free of symptoms, but has not been permitted to engage in any strenuous activities.

COMMENTS

On the basis of the electrocardiographic and vectorcardiographic data, it seems clear that this boy sustained a myocardial infarction. This is substantiated by the coronary arteriograms which demonstrated marked impairment of blood supply to the left ventricle. It is assumed that the infarction occurred with the exertion of running a race, since this is the only truly symptomatic episode admitted by the patient.

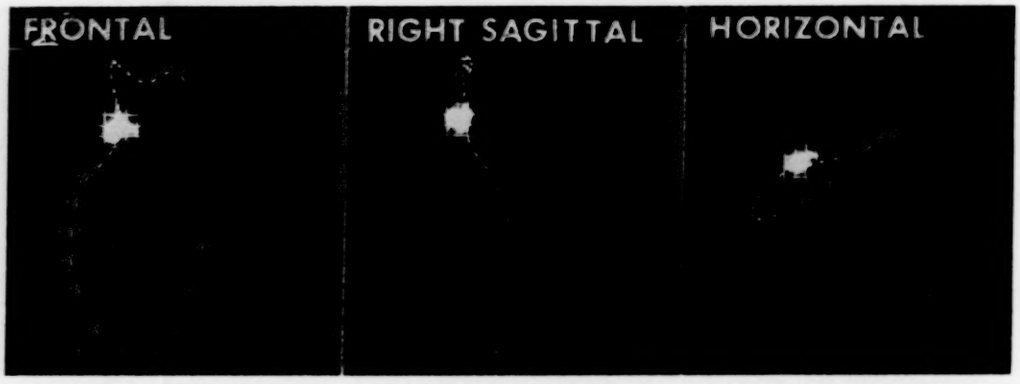

FIG. 2. Spatial vectorcardiogram, using the cube system of electrode placement. The time markings are directed with the wider ends forward. The QRS loop is in an anterior and vertical position and has a large initial anterior and rightward movement. The study was interpreted as showing a posterolateral infarction.

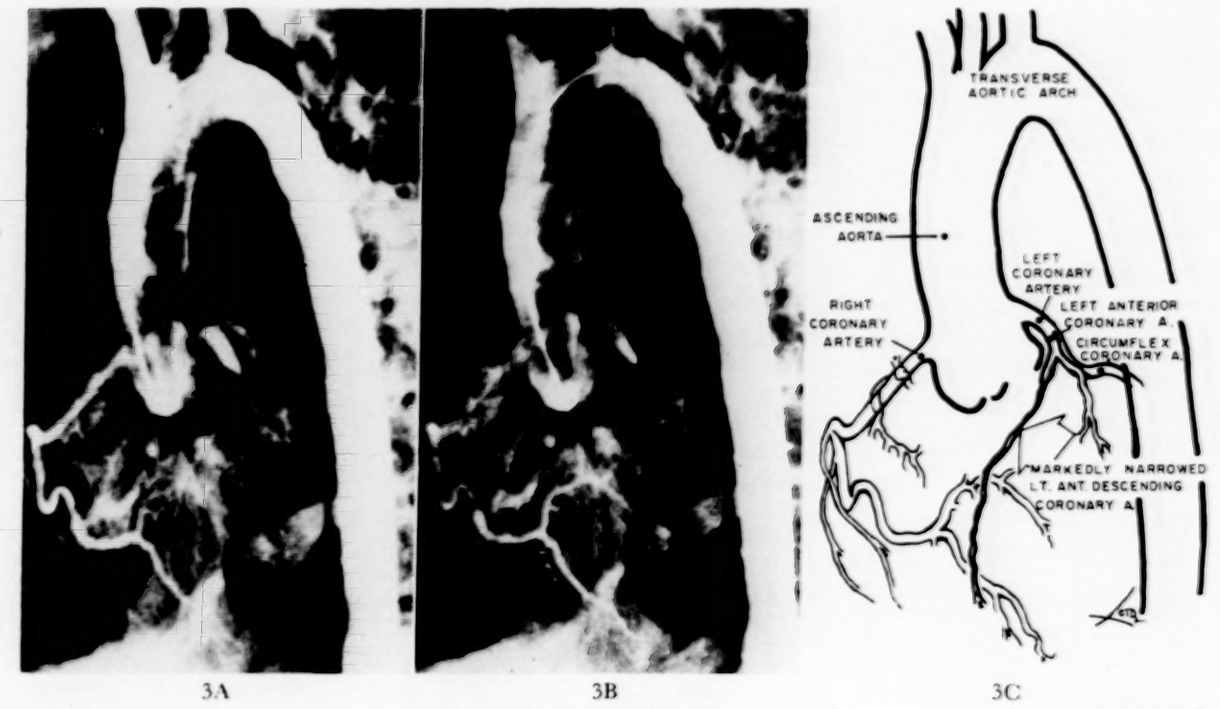

FIG. 3. Coronary arteriogram. Percutaneous retrograde femoral-aortic catheterization with injection of 30 cc. ditriokon films taken in left anterior oblique projection. A, two seconds from beginning of injection. B, one-half second later. C, composite tracing. There is marked reduction in filling of all branches of the coronary artery. The prominent narrowing of its anterior descending branch is consistent with severe atherosclerosis.

Certain causes of coronary disease in children can be excluded with reasonable certainty. Idiopathic coronary artery calcification with fibroblastic intimal proliferation, a reported cause of myocardial necrosis in infants and small children [*3–5*], is quite unlikely in view of the patient's age. Anomalous origin of the left coronary artery from the pulmonary artery rarely permits survival to the age of fifteen [*6*]. Furthermore, the arteriograms in this case clearly showed that both coronary arteries arose from the aorta.

Coronary arteritis can produce arterial occlusion through aneurysm formation and thrombosis. Polyarteritis nodosa will produce this sequence and according to Stryker can be limited to the coronary arteries [*3*]. Since this patient has survived for over a year since the acute attack, remaining entirely free of symptoms or signs of inflammatory disease, polyarteritis is unlikely. Rheumatic fever has been described as a cause of coronary arteritis although rarely, if ever, myocardial infarction [*7*]. This boy had no clinical signs of acute rheumatic fever or accompanying myocarditis. Other causes of inflammatory arterial disease, such as bacterial endocarditis and tuberculosis, lack diagnostic evidence.

The arteriograms in this patient show normal filling of the proximal portions of both coronary arteries and narrowing only after the first branching of the left coronary artery. Thus, ostial stenosis is not present. Coronary embolism is unlikely since no source of emboli was apparent, and because of the demonstration of long segments of narrowing in two major arterial branches. It is concluded, therefore, that coronary atherosclerosis is the basic disease in this patient.

Yater et al., in their extensive review of coronary atherosclerosis, found fourteen cases in patients below the age of twenty [*8*]. They and others [*9–11*] have presented autopsy evidence that coronary atherosclerosis occurs more often in young adults than generally had been appreciated. This included patients as young as eighteen. The disease can be expected occasionally to become clinically manifest in patients below this age and it is believed to be the responsible etiology in this patient. The arteriographic appearance of the involved vessels is consistent with the distribution of the disease encountered in autopsy cases.

This patient's normal blood lipid measurements and the absence of a compatible family

history exclude familial hypercholesterolemia as a predisposing factor. While the absence of chest pain in the face of serious coronary disease is unusual, several of Yater's patients experienced dyspnea and collapse as primary symptoms at the onset of acute myocardial infarction. These were the only symptoms admitted by this patient. Presumably, his coronary atherosclerosis caused insufficient restriction of coronary blood flow to produce symptoms under ordinary circumstances. With strenuous exertion, myocardial demands were not met and infarction resulted. Although coronary thrombosis cannot be excluded, it seems unlikely in view of the arteriographic findings.

SUMMARY

A fifteen year old boy, whose case is reported here, survived a myocardial infarction which was apparently related to strenuous exertion. The anatomic diagnosis, based on electrocardiographic and vectorcardiographic observations, was confirmed by coronary arteriograms which demonstrated marked narrowing of both major branches of the left coronary artery. The etiologic diagnosis of coronary atherosclerosis is suggested, primarily because of exclusion of other possibilities.

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Endobronchial Hamartoma*

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In the past two years two patients with a rare endobronchial tumor, hamartoma, have been seen at the Cincinnati Veterans Administration Hospital. The purpose of this report is to record these cases, to review the literature on the subject and briefly to discuss the clinicopathologic implications.

Case I. D. M., a thirty-six year old white man, was admitted to the Cincinnati Veterans Administration Hospital on October 7, 1957, with a complaint of chest pain and cough. There was a history of two episodes of pneumonia in 1945 and 1947, following which he noted a chronic, mildly productive cough and mild dyspnea on exertion. In the four years prior to admission he had noted worsening of these symptoms and frequent right anterior chest pain. Since 1955 he had on several occasions coughed up blood-streaked sputum.

Physical examination revealed him to be afebrile with normal vital signs. The positive findings included an increase in the anterioposterior diameter of the chest and generalized coarse rhonchi and wheezes. The laboratory findings were within normal limits except for a sputum culture of pneumococcus.

Chest roentgenogram taken on admission revealed an infiltrate with partial collapse in the upper lobe of the right lung. (Fig. 1A.) Subsequent roentgenograms revealed some clearing of the infiltrate. (Fig. 1B.) An obstruction at the origin of the bronchus of the upper lobe of the right lung was demonstrated on bronchography. Barium swallow was normal, as was fluoroscopy of the diaphragm. Bronchoscopy revealed a pink, granular tumor in the lumen of the upper lobe of the bronchus of the right lung. A lobectomy of the upper portion of the right lung was performed on December 18, 1957.

The patient made a satisfactory recovery postoperatively and chest roentgenograms taken approximately two years later revealed only residuals of previous surgery. (Fig. 1C.)

The tumor was described as wart-like, gritty to palpation and firm with an irregular surface. Microscopically, the tumor showed ossification with formation of marrow spaces and cartilage. Connective and fat tissue were also found. (Fig. 2.) The tumor was covered with pseudostratified epithelium. In some areas there was a myxomatous appearance of the interstitium.

Case II. E. G., a fifty-three year old white man, was admitted to the Cincinnati Veterans Administration Hospital on July 23, 1959, with a complaint of productive cough and right anterior chest pain since May 1959. In June the patient was hospitalized

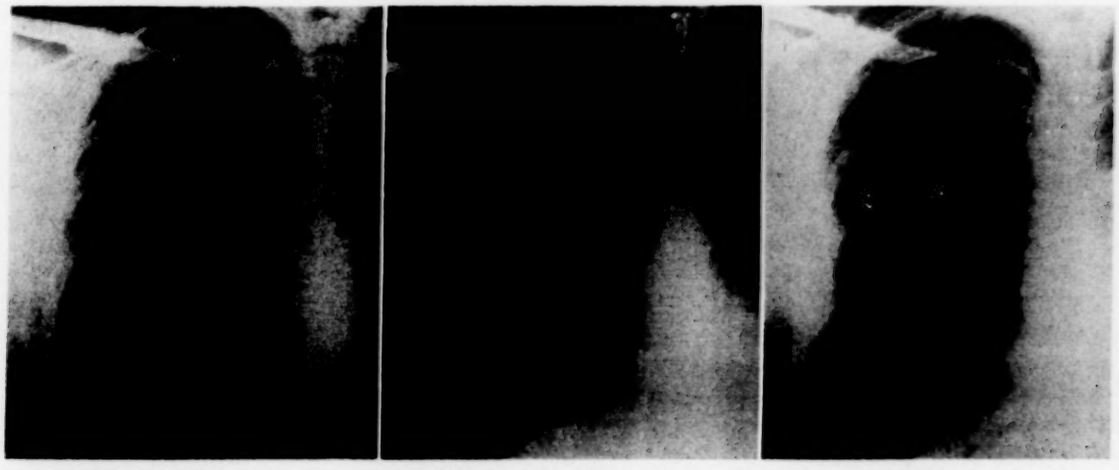

Fig. 1. Case I. Serial chest roentgenograms. Note the infiltrate in the upper lobe of the right lung with collapse in (A) and subsequent partial clearing in (B). The postoperative roentgenogram (C) shows a normal postoperative chest with the surgical rib defect.

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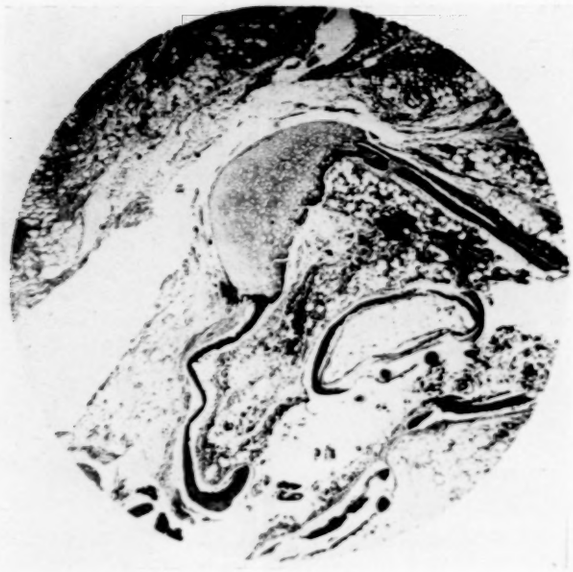

FIG. 2. Case I. Microscopic section. Cartilage and ossification with marrow spaces are evident. Connective and fatty tissue are also seen.

elsewhere, and a thoracentesis was performed. On physical examination the temperature was 100°F. (the other vital signs were normal) and there was dullness to percussion with decreased breath sounds at the right lower posterior portion of the chest. The remainder of the examination was non-contributory. The laboratory findings did not reveal any abnormalities.

A chest roentgenogram taken on admission revealed pleural fluid at the base of the right lung with a fluid level posteriorly. Laminagrams showed collapse of the middle and lower lobes of the right lung with a small empyema cavity posteriorly. A bronchogram demonstrated complete occlusion of the intermediate bronchus. Subsequent roentgenograms showed disappearance of the empyema with no change in the collapse of the middle and lower lobes of the right lung. (Fig. 3.)

The empyema was treated by tube thoracotomy and with the oral and intrapleural administration of antibiotics. Bronchoscopy was performed and a tumor was visualized in the intermediate right bronchus. Biopsy specimen showed cartilage, fat and blood vessels. The tumor was covered with respiratory epithelium. The pathologic diagnosis was hamartoma. A subsequent attempt to remove this tumor bronchoscopically was unsuccessful.

On August 24, 1959, a bronchotomy with excision of the tumor mass and re-anastomosis of the bronchus was performed. The postoperative course was uneventful. A bronchogram performed in October 1959 demonstrated normal continuity in the area of the bronchial anastomosis, but extensive bronchiectasis and collapse of the middle and lower lobes of the right lung. All bronchial orifices were patent and no tumor was seen on bronchoscopic examination in September 1959. (Fig. 4.)

The specimen consisted of a 3.5 by 1.5 cm. soft, polypoid mass attached to the bronchial wall. The cut surface was yellow and soft, with focal white areas. Microscopically, the structure was covered with columnar epithelium. There were particles of well differentiated cartilage in connective tissue and fatty tissue. The lesion was moderately vascular. (Fig. 5.)

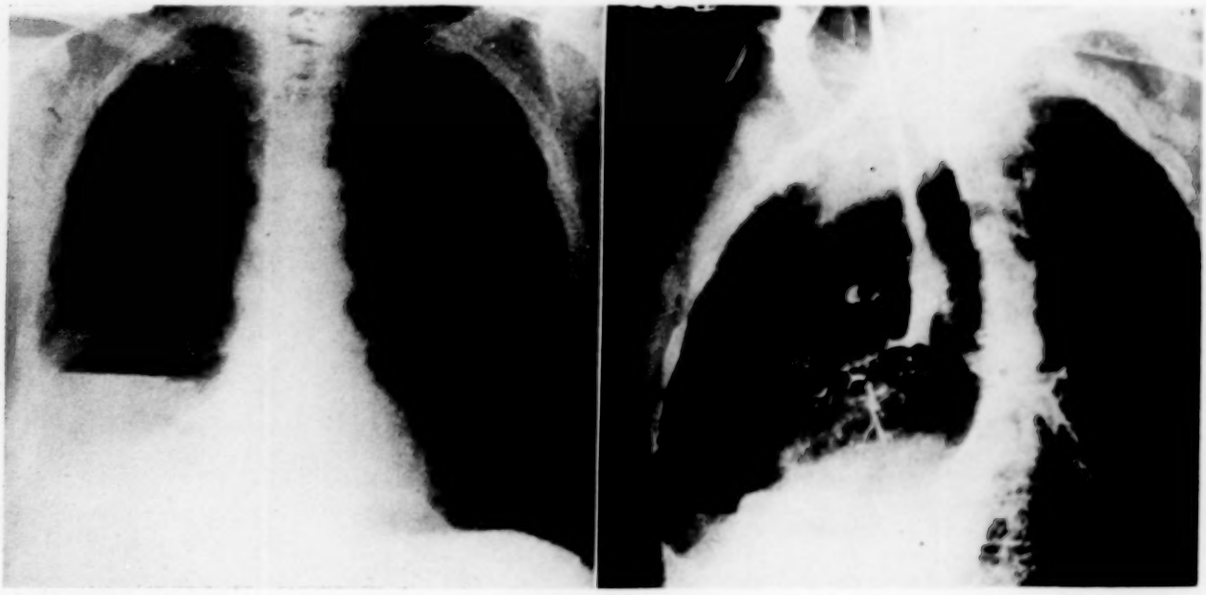

FIG. 3. Case II. Preoperative chest roentgenogram and bronchogram. An empyema cavity with an air fluid level is seen on the right. The bronchogram demonstrates complete occlusion of the intermediate bronchus.

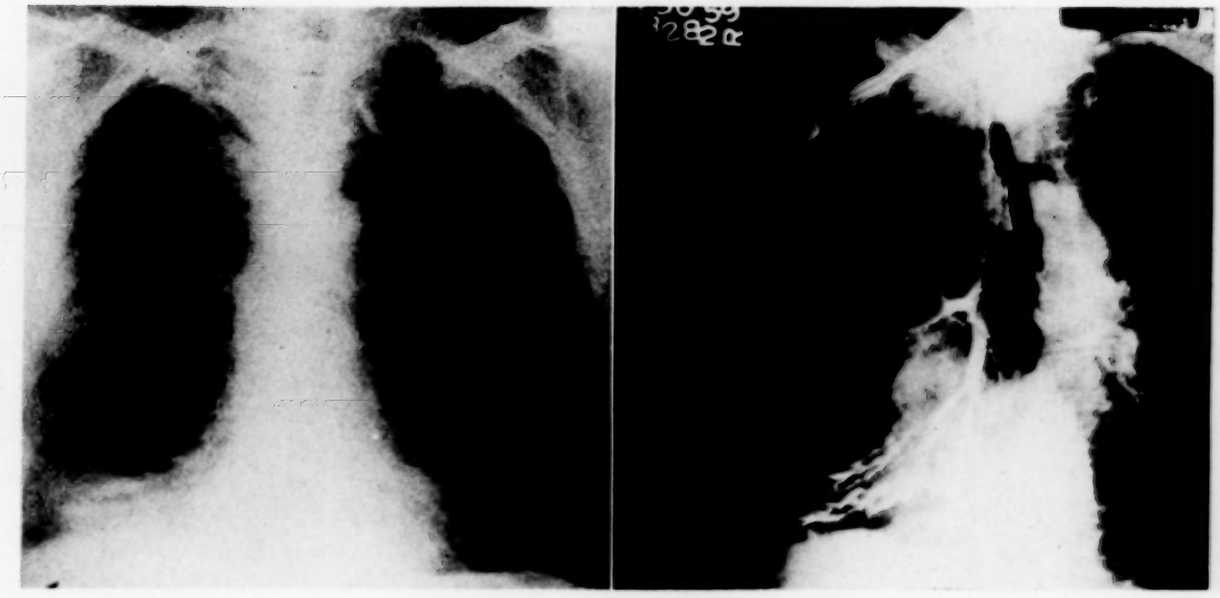

FIG. 4. Case II. Postoperative chest roentgenogram and bronchogram showing disappearance of the empyema cavity and bronchographic evidence of bronchiectasis. Note crowding together of the bronchi in the middle and lower lobes of the right lung.

Comment: The histologic diagnosis in both cases was hamartoma of the bronchus but unusual amounts of ossification of the tumor in Case I prompted consideration of other diagnoses such as choristoma and tracheopathia osteoplastica.

CLINICAL FINDINGS

A review of the reported cases of endobronchial hamartoma has been made and the significant clinical and pathologic data are presented in tabular form. (Tables I, II, III and IV.)

Analysis of the clinicopathologic data reveals the following:

Sex: In thirty-three cases recorded, twenty-seven occurred in males and six in females.

Symptoms: The most common symptom was cough, usually productive. The sputum was often blood streaked and there were several instances of gross hemoptysis. Chest pain and fever were frequently described. Weight loss occurred in several instances.

Physical signs ranged from none to those consistent with atelectasis, pneumonia and pleural fluid. Clubbing of the fingers was described in three instances [*5,6,14*].

Roentgenograms: The findings included pneumonia in the segment or lobe obstructed, pleural fluid, enlarged hilar shadows and, most commonly, collapse of the portion of the lung distal to the obstructed bronchus. Bronchography revealed the obstructing lesion in the six cases in which it was performed [*2,7,18*].

Bronchoscopy was performed in thirty-one cases and the tumor was visualized in all but three [*2,7*]. The gross appearance of these tumors

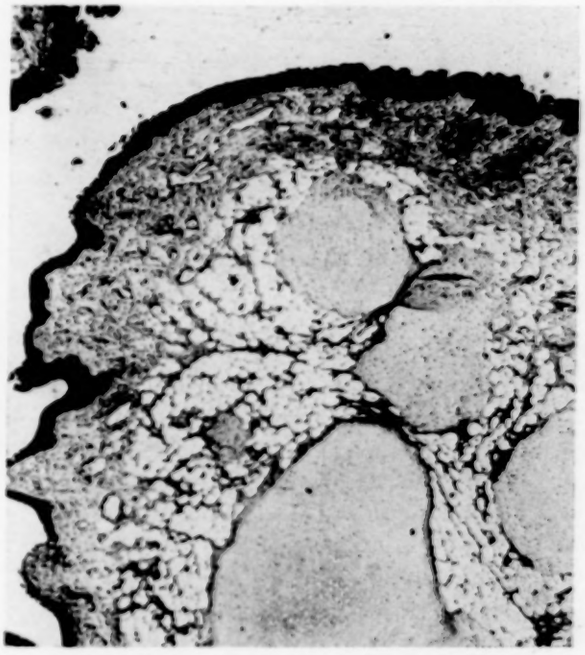

FIG. 5. Case II. Microscopic section. The polypoid nature of the tumor is seen, with its covering of columnar epithelium. Islands of cartilage are surrounded by a stroma of fatty and connective tissue.

TABLE 1
REPORTED CASES OF ENDOBRONCHIAL HAMARTOMA

Author*	Age (yr.) and Sex	Pathologic Condition
Siegert [18]	61,F	2 by 3 cm. Cartilage surrounded by connective tissue, epithelium, blood sinuses
Chiari [18]	68,F	2 by 2 cm. Cartilage, foci of calcification, fat, glands
Spuler [18]		4 cm. diameter. Cartilage, connective tissue, blood vessels
Elken [18]	41,F	1 by 6 cm. Cartilage, fatty tissue, respiratory epithelium
Blecker [18]	21,M	100 mm. diameter. Ossified cartilaginous tissue
Spiess [18]	47,F	1 by 4 cm. Cartilage, connective tissue
Caussade [18]	53,M	2.5 by 1.5 cm. Cartilage
Paul [18]	69, M	2 by 4 cm. Cartilage with myxomatous degeneration
Moore [18]	68,M	Cartilage, elastic fibers, fat
Gebauer [18]	44,M	Cartilage with calcifying plaques
Davidson [18]	66,M	Cartilage
Ulrich [18]	57,M	1 by 1 cm. Fibromyxochondrolipoma
Postlethwait [18]	57,M	1 by 1 cm. Cartilage
Sutherland [23]	52,M	4 by 5 cm. firm tumor. Elastic cartilage, connective tissue, fat, respiratory epithelium
Sutherland [23]	53,M	1.5 cm. diameter. Abundant cartilage with patchy calcification, smooth muscle, respiratory epithelium
Chardock [6]	58,M	Polypoid, pearly tumor. Lobulated cartilage separated by myxomatous tissue
Chambers [5]	48,M	1 by 1 cm., smooth with pedicle. Nodules of cartilage connective tissue, pseudostratified epithelium
Store [22]	53,M	Areas of fat, cartilage, mucin glands, transitional epithelium
Young [25]	59,M	1 by 3 cm., firm, pink. Masses of cartilage with fat, myxoid tissue, ossification, marrow, respiratory epithelium
Young [25]	62,M	1 by 3 cm., pink, polypoid. Respiratory epithelum, myxoid tissue, fat, cartilage, smooth muscle
Paterson [16]	41	Cartilage, mature fat, fibrous tissue, glands
Moersch [14]	50,F	
Moersch [14]	61,F	
Hall [10]	51,M	1 by 3 cm. yellow, smooth. Cartilage fat, muscle, respiratory epithelium, foci of calcification
Rubin [19]		
Sherrick [20]	59,M	1 by 4 cm., soft, pinkish and yellow. Islands of cartilage, adult fat, smooth muscle, glands
Effler [8]	56	1 by 2 cm., polypoid. Fat, cartilage, connective tissue, respiratory epithelium
Brewer [3]	65,M	2 by 0.7 cm., polypoid. Adipose tissue, islands of cartilage, bone with marrow
Shields [21]	61,M	0.5 by 0.5 cm., firm, pink tumor. Lobulated areas of cartilage within mesenchymal stroma, bronchial epithelium
Green [9]	62,M	1.1 by 0.6 cm., polypoid white, soft. Cartilage, glandular spaces, fat, myxomatous tissue, bronchial epithelium
Perry [17]	57,M	
Perry [17]	50,M	Smooth, pale, lobulated. Cartilage, epithelial elements
Donoghue [7]	60,M	1 by 1 cm., polypoid
Donoghue [7]	39,M	Myxomatous cartilage
Dovenbarger	53,M	3.5 by 1.5 cm., polypoid, soft. Masses of cartilage, fibrous tissue, fat
Dovenbarger	36,M	Wart-like, firm, pink. Cartilage with ossification, bone marrow spaces, fat, connective tissue
Carlsen [4]	1 case	
Bleyer [2]	5 cases	

* The first thirteen cases are those tabulated by Postlethwait in 1948.

TABLE II
CLINICAL DATA IN THIRTY-TWO CASES OF ENDOBRONCHIAL HAMARTOMA

Clinical Findings	No. of Cases
Cough	27
Hemoptysis	11
Fever	8
Dyspnea	6
Chest pain	6
Wheezing	4
Weight loss	3
Clubbing	3

was varied, the color ranging from pink to yellow to bluish red and surface characteristics from smooth to lobulated to papillary. Localization was in a major or lobar bronchus in all but four instances: three of these were in segmental bronchi [*18,20,21*] and one was in the trachea [*17*].

The dimensions of the tumors ranged from 0.5 by 0.5 cm. to 4 by 3 cm; and the consistency from soft to firm, depending upon the relative amounts of cartilage, fat and connective tissue. Microscopically, areas of cartilage were universally seen, with adipose and fibrous connective tissue usually associated. Myxomatous tissue was commonly found, as was respiratory epithelium. Bronchial glands and smooth muscle were seen in several tumors and foci of calcification were not uncommon. Ossification was described in three instances. In two reports [*5,7*] the cartilage within the tumor appeared to be continuous with the normal bronchial cartilage.

Treatment: Thirty-four of the thirty-seven patients were treated surgically, fourteen by lobectomy, ten by bronchoscopic removal [*10,14,17,18*], six by pneumonectomy, two by transpleural bronchotomy [*5*], one by segmental resection and one by empyema drainage. Most investigators agree that the ideal method of treatment is bronchoscopic removal or bronchotomy and excision. However, irreversible distal pulmonary parenchymal changes secondary to infection often necessitates removal of the affected portion of lung. Consideration of carcinoma also contributed to the frequency of lobectomy and pneumonectomy.

In the cases presented here, lobectomy was performed in the first case because of the unknown nature of the tumor. It seems possible that simpler measures might have been effective.

TABLE III
ROENTGENOGRAPHIC FINDINGS IN TWENTY-SIX CASES RECORDED

Findings	No. of Cases
Atelectasis	13
Infiltrate	10
Hilar prominence or mass	5
Fluid	2
Visualization by bronchography	6

Case II illustrates that if transpleural bronchotomy is contemplated, consideration must be given to the status of the distal bronchi in order to avoid leaving bronchiectatic areas in situ. In this case, the areas of lung below the obstruction were described as "normal" at the time of surgery.

GENERAL DISCUSSION

Hamartoma of the lung (synonyms being adenochondroma, adenofibrolipochondromyxoma, chondroma and lipochondroadenoma) is a well known entity. The microscopic picture of pulmonary hamartoma, it is generally agreed, consists of a stroma made up of masses or lobules of cartilage surrounded by connective tissue, both fibrous and myxomatous. Adipose tissue is frequently found scattered in the connective tissue and respiratory epithelium is found covering the lobules and lining cleft-like spaces. Glandular elements, smooth muscle, and foci of calcification and ossification may be seen [*13,19*]. There may be histologic variation with predominance of any of the various elements, explaining the many descriptive synonyms.

TABLE IV
LOCATION BY BRONCHOGRAPHY (SIX CASES) OR BRONCHOSCOPY (TWENTY-EIGHT CASES)

Bronchus	No. of Cases
Right main	4
Left main	6
Upper lobe of left lung	3
Upper lobe of right lung	2
Intermediate	3
Lower lobe of right lung	4
Lower lobe of left lung	3
Middle lobe of right lung	2
Trachea	1
Segmental bronchi	3

The term "hamartoma" is a general one and is applied also to tumors found in many organs other than the lungs. Albrecht [*10*] in 1904 defined hamartoma as "tumor like malformations in which occurs only an abnormal mixing of the normal components of the organ. The abnormality may take the form of a change in quantity, arrangement or degree of differentiation, or may comprise all three. The deduction to be drawn from histologic examination of the formations is that they have originated in an abnormal mixing of the elements or from disturbances of their development."

The hamartoma is now generally agreed to be developmental in origin, but other theories of etiology postulated have included hyperplasia of normal structures, neoplasia, inflammation and metaplasia of normal bronchial connective tissue into cartilage and adipose tissue [*8,23*]. It has been postulated that localized changes in the arrangement, quantity or differentiation of the bronchial components during embryologic development could produce the hamartoma. Some favor the embryonic anlage theory of origin because of the presence of elastic fibers in the cartilage of hamartoma, which are not found in normal bronchial cartilage [*6*].

Hamartoma of the lung is usually considered in the differential diagnosis of solitary, circumscribed pulmonary nodules and is not uncommon, as indicated by the series from the Mayo Clinic in which 16 per cent of the solitary nodules resected were hamartomas [*12*]. In recent years there have been increasing numbers of case reports describing hamartomas in an endobronchial location, producing signs and symptoms of bronchial obstruction. The peripheral, circumscribed type of hamartoma rarely produces symptoms unless, by proximity to small bronchi, it causes obstruction. Histologically, the endobronchial variety of hamartoma is composed of the same mesodermal and epithelial elements as the peripheral type, but arises within the bronchial wall. Sutherland et al. believe that the endobronchial and peripheral varieties differ only in their location, the peripheral type arising from smaller bronchi [*23*]. No bronchial attachment can be identified in many cases of peripheral hamartoma, but cases are described in which there is a definite origin from the connective tissue of small bronchi and bronchioles [*11,24*].

There is controversy as to the differentiation between chondroma of the bronchus and endobronchial hamartoma. Muendal et al. [*15*] believe that chondroma and hamartoma may be the same tumor with minor variations but Liebow [*13*] contends that chondroma does not contain the admixture of connective tissue found in hamartoma.

Postlethwait et al. in 1948 reported one case of endobronchial hamartoma and found twelve cases recorded earlier in the literature [*18*]. Since then a number of case reports and reviews have appeared [*2–11,14,16,17,19–23,25*]. Analysis of figures from these reports suggests an endobronchial location in 8 to 20 per cent of clinically manifest pulmonary hamartomas.

The location of the tumor in one of the previously reviewed cases [*1*] was not truly endobronchial, so we have excluded this case from our review. The acceptable cases plus the two cases reported herein combine to make a total of forty-two cases of endobronchial hamartoma reported.

Hamartoma of the bronchus is thus one of the benign bronchial tumors that infrequently are causes of bronchial obstruction. Fibromas, lipomas and chondromas are the other common members of this group [*7,13*]. There is no clinical syndrome that would differentiate hamartoma from other causes of bronchial obstruction. The average age of occurrence was in the group in which bronchogenic carcinoma is commonly seen and the symptomatology, roentgenologic findings and bronchoscopic examination were often indistinguishable from carcinoma. However, when differentiation can be made by bronchoscopic biopsy simpler surgical treatment will suffice in lieu of the more extensive pulmonary resections employed when malignancy is present.

SUMMARY

Two cases of endobronchial hamartoma are reported, making a total of forty-two noted in the British and American literature. Although uncommon, hamartoma should be given consideration in any case manifesting bronchial obstruction.

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Macronormoblastic Hyperplasia of the Bone Marrow in Hepatic Cirrhosis*

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DESPITE the frequency of anemia in patients with hepatic cirrhosis [*3,6,9,10,11*], the common occurrence of a macronormoblastic hyperplasia in the bone marrow has received meager recognition [*1,8*]. Because of a remarkable similarity between macronormoblasts and megaloblasts the bone marrow changes in cirrhosis have occasionally been mistaken for megaloblastic hyperplasia of the pernicious anemia type [*4,6*]. Patients who manifest symptoms related to their anemia rather than to liver dysfunction may therefore pose a difficult diagnostic problem. This is the report of such a case, with a review of the literature concerning macronormoblastic hyperplasia.

CASE REPORT

A fifty-nine year old white woman was admitted to the hospital on January 5, 1959, because of progressive swelling of the lower extremities and lower abdominal wall of six months' duration. She complained of diarrhea for the past two months, but denied any unusual stool color. The review of systems revealed nervousness, occasional paroxysms of palpitation and nocturia. She had no recent weight loss. Her alcohol consumption consisted of several cocktails per night. The patient had never been pregnant. Menopause occurred at forty-five years of age. The family history was non-contributory.

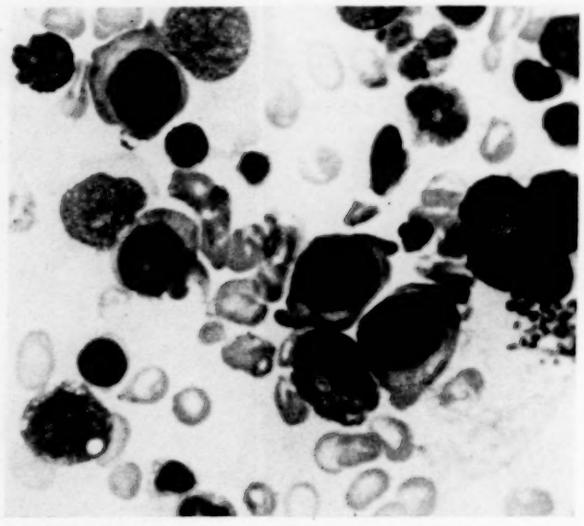

FIG. 1. Sternal bone marrow aspirate, macronormoblastic hyperplasia. Two macronormoblasts in lower right and one in upper left portion of field. Note comparative size of normal intermediate and late normoblasts. Original magnification × 475.

Physical examination revealed a moderately obese white woman with blood pressure 190/170 mm. Hg, pulse 100 per minute, respirations 20 per minute and temperature 99°F. She was pale but not icteric. The hair was thin and grey. There was marked pitting edema to the level of the knees. There was apparent cardiac enlargement and a grade 1 systolic aortic murmur. The liver edge was palpable 5 cm. below the costal margin. The spleen and kidneys were not palpable. The deep tendon reflexes were hyperactive.

Roentgenograms showed multiple diverticulae of the sigmoid colon, a small calcified nodule in the upper lobe of the right lung, and changes compatible with antral gastritis.

The hemoglobin was 7.8 gm. per cent, hematocrit 26 per cent, total white cell count 6,000 per cu. mm. with 84 per cent neutrophils, 6 per cent bands, 4 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils and 1 per cent myelocytes. The peripheral blood showed macrocytosis with moderate anisocytosis and poikilocytosis. A peripheral blood study on January 7, 1959, revealed a hemoglobin of 8.5 gm. per cent, hematocrit 25 per cent, red blood cell count 2.4 million per cu. mm., and reticulocyte count 1.8 per cent. The red blood cell indices showed a mean corpuscular volume of 105 cu. μ, mean corpuscular hemoglobin concentration 33 per cent, mean corpuscular hemoglobin 34 $\mu\mu$g. The direct platelet count was 356,000 per cu. mm.

Smears of a bone marrow aspirate revealed a marked erythrocytic hyperplasia. All stages of normoblasts were increased in number. There were numerous large erythrocytic cells having abundant basophilic cytoplasm and fairly large nuclei with chromatin patterns resembling pronormoblasts. (Fig.

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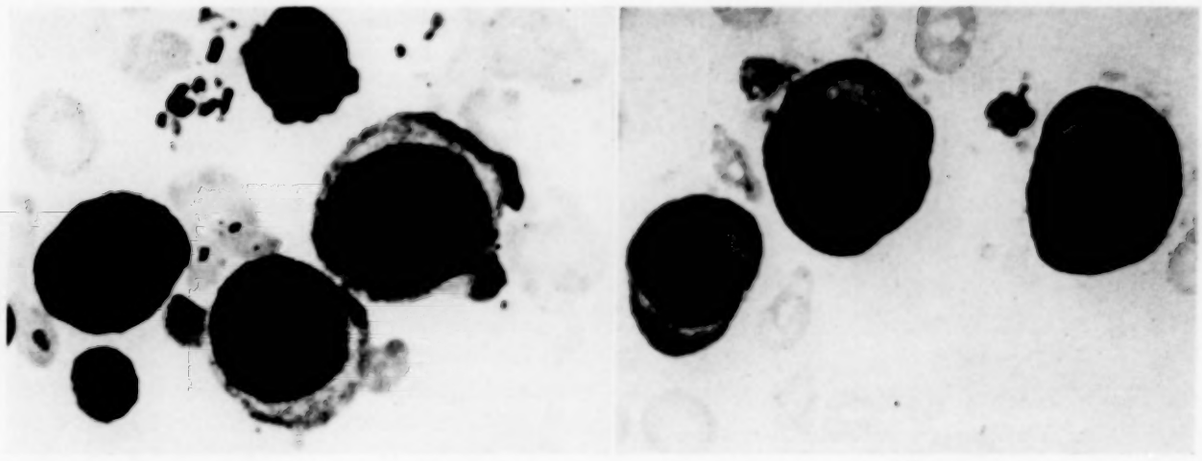

2A 2B

FIG. 2. Original magnification × 2,000. A, bone marrow aspirate, macronormoblasts. Note homogeneous chromatin pattern with minimal clumping. B, bone marrow aspirate, megaloblasts (pernicious anemia). Note fine skein-like chromatin pattern.

1.) Many cells in the erythrocytic and granulocytic series bore a strong resemblance to pernicious anemia type cells except for a slightly coarser nuclear chromatin structure. (Figs. 2A and 2B.) A Schilling test revealed 22 per cent radiocobalt B_{12} excreted in the urine in twenty-four hours.

Additional laboratory data included a total serum protein of 5.9 gm. per cent, albumin 3.9 gm. per cent, alkaline phosphatase 2.1 Bessey-Lowry units, cephalin flocculation test negative, thymol turbidity test 3 units, serum bilirubin 1.3 mg. per cent, bromsulphalein retention 41 per cent in one-half hour. The prothrombin activity was 35 per cent and rose to 70 per cent following the administration of vitamin K. The serum glutamic oxalacetic transaminase was 19 units, serum glutamic pyruvic transaminase 11 units, serum iron level 140 gamma per cent, total iron binding capacity 195 gamma per cent. The serum electrophoretic pattern showed a low albumin; the globulin fraction was within normal limits. The stool occult blood was positive (benzidine). Gastric analysis showed no free hydrochloric acid with histamine stimulation; total acid was 11°.

The patient was treated with folic acid, vitamin B_{12} and vitamin C, along with a high caloric diet and blood transfusions. Her reticulocyte count reached 6.4 per cent on January 27 and the hemoglobin 12.4 gm. per cent. On January 22 the patient had considerable diarrhea with abdominal distention and a temperature of 102°F., for which she received antibiotics and fluids. There was apparent ascites but paracentesis yielded only 200 cc. of serous fluid. A blood ammonia at this time was 321 μμg. per cent. Pulmonary edema developed and the patient was digitalized on February 13. Three days later she died in a state of dyspnea, restlessness and stupor.

At autopsy the body was that of a well developed and moderately obese white woman with marked edema of the lower extremities and abdominal wall. There was no icterus. The abdomen was distended. On the anterior wall there was an 18 cm. right paraumbilical scar and a recent suprapubic paracentesis incision. Scattered superficial ulcers were noted over the sacrum. The peritoneal cavity contains 3,200 cc. of serous fluid. The pleural cavities contained 250 cc. of clear fluid on the right and 100 cc. on the left. The heart was symmetrically enlarged and weighed 480 gm. The left ventricle measured 1.5 cm. in thickness and the right ventricle 0.4 cm. The left lung weighed 460 gm. and the right lung 660 gm. There was edema with patchy areas of congestion in the lower lobes. The liver weighed 1,620 gm. The capsular surface was red-brown with slight fine nodularity. The cut surfaces were yellow-tan and moderately firm. The spleen weighed 220 gm. The kidneys had a finely granular surface, each weighing 150 gm. There was a small prepyloric ulcer on the lesser curvature of the stomach. The arteries of the circle of Willis showed moderate atherosclerosis. The remaining organs appeared normal.

On microscopic examination the liver showed active cirrhosis of a type difficult to classify. (Fig. 3.) Some areas suggested portal cirrhosis characterized by pseudolobulation, periportal fibrosis extending into the lobules, moderate fatty metamorphosis, bile duct proliferation, increase in mononuclear inflammatory cells, and alternating areas of degeneration and regeneration of hepatic cords. In several sections, however, the fibrosis was more diffuse and there was little evidence of pseudolobulation. These areas suggested a so-called diffuse cirrhosis [7]. The bone marrow sections showed foci of erythroid hyperplasia and a reduced number of bony trabeculae. There were scattered foci of extramedullary hemopoiesis in the

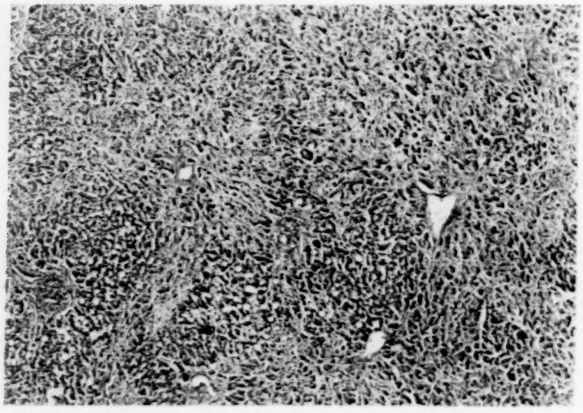

FIG. 3. Liver, cirrhosis (autopsy specimen). The lower portion shows pseudolobulation and fatty metamorphosis, while the upper portion shows more diffuse fibrosis. Original magnification × 56.

spleen. Myelin sheath stains on the cervical, thoracic and lumbar spinal cord sections showed no degeneration of the posterior column.

COMMENTS

The predominant disease process in the patient was hepatic cirrhosis. In the absence of any other likely etiology, the severe macrocytic anemia was considered to be secondary to chronic liver disease. The apparent cause of death was hepatic insufficiency and terminal congestive heart failure.

Anemia associated with cirrhosis may be either macrocytic or normocytic but not hypochromic unless hemorrhage is a complicating factor. In a study of 132 cases of liver disease Wintrobe [*10*] found that the incidence of macrocytic anemia in cirrhosis was 36.6 per cent. The figures cited by Berman from his own work and from the literature vary from 9 to 92 per cent. Wintrobe states that macrocytic anemia occurs when damage to the liver is particularly severe and diffuse. Berman found no correlation between the severity of anemia and the grade or degree of cirrhosis. Cheney [*2*] suggested that the tendency to macrocytosis is proportional to the degree of anemia and not to the degree of jaundice.

The bone marrow is usually hypercellular in cirrhosis, in contrast to the erythropoietic depression found in many toxic conditions. Although reported in some instances as a megaloblastic anemia similar to pernicious anemia [*4,6*], recent investigations have tended to distinguish the bone marrow changes as macronormoblastic in many cases of cirrhosis [*1,8*]. While the presence of cirrhosis suggests a possible defect in the antipernicious anemia mechanism or other nutritional factors, this has yet to be proved. Some of the findings in the case cited, e.g. a slightly elevated serum bilirubin and a moderate reticulocytosis, suggest an increased rate of erythrocyte destruction as the basic difficulty. Berman [*1*] cites numerous authors who have categorically denied the presence of megaloblasts in the bone marrow of patients with cirrhosis of the liver. The degree of anemia is not usually as severe as in pernicious anemia; however the mean corpuscular volume, the tendency towards remission, response to liver therapy and the presence of extramedullary foci of hemopoiesis in the spleen are similar. Achlorhydria is frequently not present.

The characteristics of macronormoblasts have been described by Jones [*5*] and Berman [*1*], particularly with regard to their distinction from megaloblasts. The mean diameter of macronormoblasts is increased and the nucleocytoplasmic ratio is altered in favor of a relative increase in cytoplasm. The absolute increase in cytoplasm is not as marked as seen in megaloblasts. The nuclear pattern in the macronormoblasts is essentially that of physiologic normoblasts. In some of Berman's patients the normoblasts showed a nuclear structure similar to that of reticulum cells. According to Jones, giant band forms of neutrophils and giant polymorphonuclear neutrophils with hypersegmented nuclei are sometimes seen, but there is no marked change in the type of granulation nor is the chromatin pattern of the nuclei as fine as seen in the typical dysplastic cells associated with megaloblastic marrows. The associated changes of anisocytosis and poikilocytosis are apparently not present or absent with sufficient regularity to be of value in distinguishing the macrocytic anemia of cirrhosis from other diseases. The leukocytes do not appear affected in respect to total number although an absolute lymphopenia was one of the most constant significant alterations of the peripheral blood described by Berman. Thrombocytes are usually in the low or low normal range. A distinct hemorrhagic tendency has been observed in some cirrhotic patients regardless of the absolute platelet picture [*1*].

Although these features are useful in distinguishing macronormoblastic hyperplasia from megaloblastic hyperplasia, histodiagnostic errors are probably common in the absence of sufficient clinical data. In patients manifesting achlorhydria, peripheral macrocytosis and macro-

erythrocytic precursors in bone marrow smears, the Schilling radiocobalt B_{12} absorption test is helpful in ruling out pernicious anemia. If cirrhosis is present, the combination of liver function tests and liver biopsy will yield a definitive diagnosis in practically every case.

Macronormoblastic hyperplasia is not a pathognomonic finding and probably occurs in many conditions characterized by active erythropoiesis [8]. It is interesting to consider the relationship between the macrocytic anemias caused by outpouring of reticulocytes into the peripheral blood and those resulting from larger erythrocytic precursors. In many cases this is probably a matter of the duration and severity of the anemia rather than a real difference. It has been our experience that in most macrocytic anemias, not associated with megaloblastic hyperplasia, an adequate search will usually reveal macronormoblasts in the bone marrow smears. Nevertheless, an unexplained macronormoblastic hyperplasia should alert the hematologist to the possibility of an obscure hepatic cirrhosis.

CONCLUSION

A case of hepatic cirrhosis associated with severe anemia and macronormoblastic bone marrow hyperplasia is reported. The literature concerning the occurrence of anemia in hepatic cirrhosis is briefly reviewed and certain points which may be helpful in distinguishing between macronormoblastic and megaloblastic anemias are presented.

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Fibrosis of Central and Hepatic Veins, and Perisinusoidal Spaces of the Liver Following Prolonged Administration of Urethane*

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SINCE its introduction into the treatment of multiple myeloma thirteen years ago [*1*], urethane (ethyl carbamate) has become the major chemotherapeutic agent used in the treatment of this disease [*2*]. The primary side effects of urethane are unpleasant gastrointestinal symptoms and (generally reversible) bone marrow depression resulting usually in leukopenia and thrombocytopenia [*2*]. In addition, the hazard of hepatic toxicity has been recognized [*2*]. A pathologic alteration in the liver that has often been attributed to urethane toxicity is centrolobular necrosis resulting in death within a few weeks after the first signs of hepatic insufficiency [*3–7*]. Such a pathologic change, however, can be quite non-specific; it is known that the liver is extremely sensitive to oxygen deficiency and pressure effects, and centrolobular necrosis can be found at autopsy simply as a result of agonal processes unrelated to the actual disease or drug toxicity [*8*].

Meacham, Tillotson and Heinle [*9*] described a patient in whom the pathologic changes in the parenchyma of the liver appeared to be secondary to rather unique vascular changes produced by the administration of urethane. Death occurred within two weeks of the onset of the first symptoms of hepatic disease. The patient presented herein is another example of possible urethane toxicity of the liver resulting primarily from a direct vascular effect. In this instance death did not occur until four months after the onset of the symptoms of liver toxicity. It is therefore believed that the pathologic changes described represent a chronic manifestation of urethane toxicity affecting the liver.

CASE REPORT

Patient E. B. (No. A–117–59), a forty-four year old Negro woman, was admitted to the hospital of the Brookhaven National Laboratory for the first time on January 30, 1958. Her present illness dated back to July 1957, at which time severe pain over the lumbar spine, weight loss, epistaxis and bleeding gingiva gradually developed. By December 1958 she had required three blood transfusions in another hospital and was incapacitated by the back pain.

Physical examination on the first admission was essentially within normal limits except for limitation in movement due to back pain. Pertinent laboratory studies on admission were: hematocrit 21.1 per cent; hemoglobin 7.3 gm. per cent; leukocyte count and differential were within normal limits. The platelet count was 180,000 per cu. mm. The blood urea nitrogen was 29.3 mg. per cent, serum total proteins 12.5 gm. per cent, albumin was 1.9 gm. per cent, globulins 10.6 gm. per cent. The prothrombin time was 31.2 per cent of normal. The serum total bilirubin was 0.18 mg. per cent, the alkaline phosphatase was normal. Serum calcium was 11.2 mg. per cent. Coombs' direct and indirect test was negative. Urinalysis was negative. Bence Jones protein was not found in the urine. A skeletal survey revealed diffuse osteoporosis.

Bone marrow aspiration confirmed the diagnosis of multiple myeloma. Treatment consisted of multiple blood transfusions.

During the Spring of 1958 she was repeatedly admitted to the Brookhaven National Laboratory, Medical Research Center, primarily because of severe back pain, epistaxis, bleeding gingivae, and anemia requiring blood transfusions. A bromsulphalein test in April 1958 showed 10 per cent retention of dye in forty-five minutes. The cephalin flocculation and thymol turbidity tests were again within normal limits. Following the institution of prednisone therapy

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in May 1958, there was marked subjective improvement but no evidence of an objective remission. The serum total proteins at this time and, in particular, the globulins remained elevated. The serum calcium was 12 mg. per cent. Results of tests for Bence Jones protein and cryoglobulins remained negative. Electrophoresis demonstrated a typical myeloma pattern of the gamma type.

By July 1958 the patient was completely bedridden by severe back pain. Urethane therapy was started and the initial dose of 3.6 gm. per day was rapidly increased to 6 gm. per day. Within six weeks subjective and objective improvement was noted. The back pain had decreased, and the patient was able to sit up in bed. The serum total proteins had declined to 9.1 gm. per cent, the albumin had risen to 2.8 gm. per cent, the globulins were 6.3 gm. per cent, and the serum calcium had fallen to 9.9 mg. per cent. A marrow aspiration performed on August 27, 1958, revealed a marked increase in both erythroid and myeloid activity. The patient was discharged from the hospital on a maintenance dose of 0.9 gm. of urethane four times a day; therapy was continued until May 31, 1959. Serum albumin and globulin studies and a bone marrow aspiration performed in January 1959 again showed evidence of partial objective remission.

Readmission to the hospital was required in May 1959 because of the sudden development (within seven days) of marked painless abdominal distention that was associated with malaise and a low grade fever. The pertinent physical findings on admission were a sinus tachycardia (130 per minute) and ascites. The serum total bilirubin was 2.2 mg. per cent, the cephalin flocculation was 3 plus in forty-eight hours, the prothrombin time was 28.6 per cent of normal. The serum total proteins were 8.6 gm. per cent with albumin 1.9 gm. per cent and globulins 6.7 gm. per cent. Thymol turbidity was elevated. The serum alkaline phosphatase was normal (10 King-Armstrong units).

Even though the patient had significant benefit from the urethane therapy, manifested by no blood transfusion requirement for a year, improvement in well being and a partial reversion of abnormal chemical findings, the urethane (after a total dose of 1,100 gm.) was discontinued because of the hepatic injury presumably due to urethane toxicity. Upon hospitalization and discontinuance of urethane the jaundice cleared. However, there was little improvement in the ascites despite vigorous attempts at diuresis by the administration of mercurials and chlorothiazide (Diuril®).

She was discharged on July 11, 1959, on a regimen of 10 mg. of prednisone per day and Diuril. An exacerbation of the myeloma process was indicated by the falling hematocrit and increasing back pain. Urethane therapy was commenced again in July 1959 at a dosage of 3.6 gm. per day. However, this therapy was stopped on August 7, 1959, because of fear of further hepatic damage. The total dose of urethane was then 1,180 gm.

Readmission was necessary again in November, 1959 because of persistent ascites and severe low back pain, bronchopneumonia and bilateral otitis media. The infections responded promptly to antibiotic treatment and large doses of corticosteroids administered in order to counteract possible relative adrenal insufficiency. Following the subsidence of the pneumonia in about one week, deep x-ray radiation to the lumbar spine was given and Nilevar® (norethandrolone, 20 mg. per day) started in an attempt to obtain symptomatic relief from the back pain. The ascites was treated with a low salt diet, frequent injections of mercurial diuretics and a daily dose of 1 gm. Diuril. During this period the patient received supplementary potassium. A bromsulphalein test revealed 28 per cent retention in forty-five minutes. On November 21, 1959, the patient became semicomatose and within forty-eight hours a flapping tremor of both hands and a coarse tremor of the tongue developed, the early stages of hepatic coma. The administration of Nilevar, Diuril and mercurial injections were immediately discontinued and treatment with Chloromycetin,® Mycostatin® and vitamins was instituted. A complicating urinary tract infection due to Escherichia coli responded satisfactorily to Chloromycetin. The patient improved rapidly and within a week was again entirely oriented and alert. However a falling platelet count and increasing numbers of plasma cells in the peripheral blood indicated deterioration in the myeloma process.

Serum transaminase (SGOT), alkaline phosphatase and bilirubin (direct and indirect) determinations remained normal throughout the admission. Thymol turbidity was 13.6 Maclagan units. A cephalin flocculation test prior to the onset of the hepatic coma was three plus after forty-eight hours. Plasma proteins and a repeat electrophoresis did not show any significant changes. Ultracentrifugation revealed no abnormal macroglobulins. A repeat bromsulphalein test on the day of discharge, December 17, 1959, showed 27 per cent retention in forty-five minutes.

An interesting development on this admission was a definite decrease in the ascites that coincided with the institution of increased steroid therapy. This improvement persisted even after the administration of Diuril and mercurial diuretics were stopped.

The patient was readmitted for the last time on December 23, 1959, in hepatic coma with severe bleeding from the nose and rectum. A complicating septicemia due to a Chloromycetin-sensitive E. coli was treated with large doses of Chloromycetin and hydrocortisone. The patient did not respond to treatment and died on December 26, 1959, in hepatic coma after Jacksonian seizures on the left side developed. On the day of death the SGOT was 20.6 units and the serum bilirubin also was normal.

At autopsy there was no jaundice. About 2,000 ml.

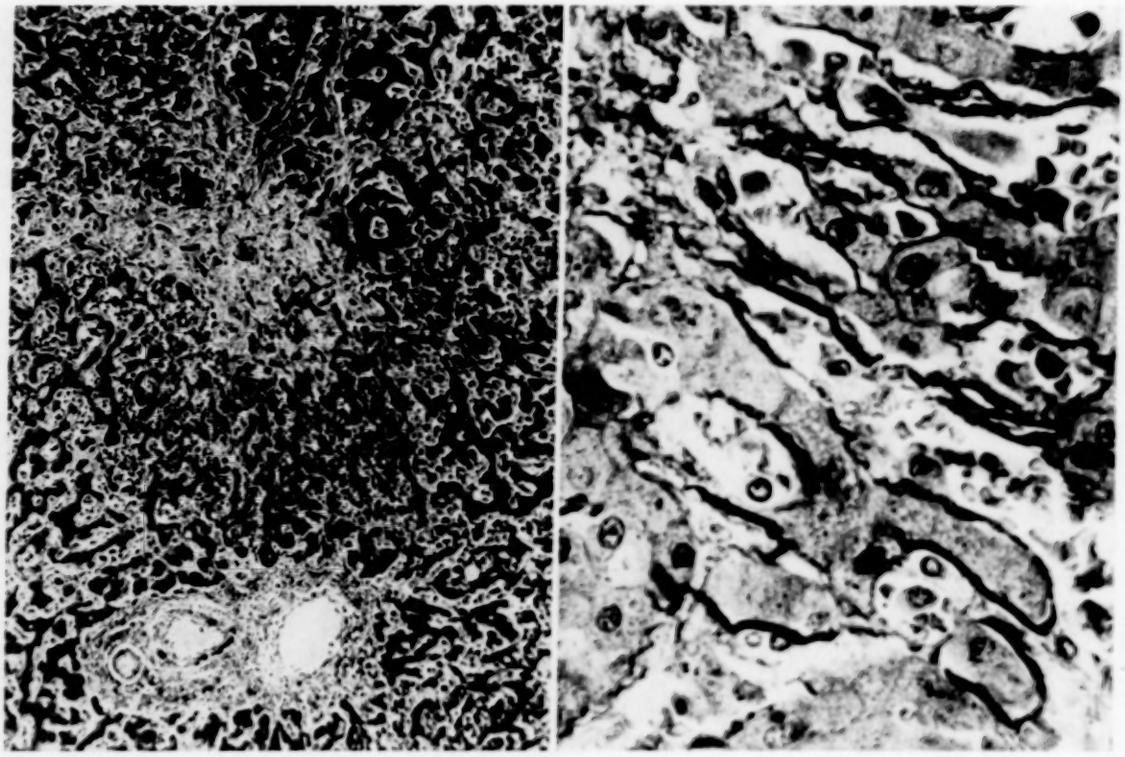

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FIG. 1. Section of liver showing fibrous obliteration of a central vein with minimal involvement of adjacent portal area. Masson's trichrome stain.

FIG. 2. Higher magnification showing the increase in perisinusoidal connective tissue. Van Gieson collagen stain.

of clear yellow ascitic fluid were removed from the peritoneal cavity. The liver weighed 1,450 gm. and, except for blunting of the edges, was of normal size and shape. It was yellowish brown with a firm consistency and a uniform, finely granular surface. The lobular pattern was less distinct than usual. There were no abnormalities of the gallbladder or gallbladder bed. Microscopically, the architecture of the liver was distorted by a diffuse fibrosis, and well defined central veins were rarely seen. Fibrous tissue formed fine, irregular bands and small islands which did not usually involve the portal areas but more often the central portions of the lobule. (Fig. 1.) The most significant change was an extensive fibrosis in and around the branches of the hepatic vein that extended into the central veins and perisinusoidal spaces. In most but not all regions studied, the spaces of Disse contained mature fibrous tissue. (Fig. 2.) In some instances the sinusoids were completely obliterated. The parenchyma cells of the liver were reduced and atrophic in some areas, but there was no severe hepatocellular necrosis or fatty metamorphosis. There were some areas of patchy degeneration and regeneration of liver cells associated with mobilization of neighboring reticuloendothelial cells that were frequently pigmented. There were some regions of bile stasis within liver cells, accompanied by occasional bile plugs in the cholangioles. Large numbers of reticulum cells and their apparent derivatives as well as plasma cells were noted in the sinusoids and in the perisinusoidal spaces.

The spleen was enlarged, weighing 320 gm. and had a resilient consistency. The histologic changes were those of chronic passive congestion. There was chronic hydronephrosis of the left kidney and an associated hydroureter which extended down to its entrance into the bladder. The pelvis and ureter were distended with clear yellow fluid. The left kidney weighed 60 gm. The right kidney weighed 240 gm. and was grossly and histologically normal. No precipitate was found in the tubules, and the tubular epithelium showed none of the changes often associated with multiple myeloma.

Bone marrow of ribs, sternum and vertebrae was largely replaced by plasma cells.

The ovaries and uterine fundus were absent (surgically). It is possible that the hydroureter on the left was secondary to the hysterectomy in 1955.

Focal collections of petechiae were present in the cerebral cortex of the right frontal lobe and in the pons. There were no other significant pathologic findings.

COMMENTS

In animal experiments the primary histologic lesion of the liver in acute urethane toxicity is reported to be a vascular one. Doljanski and Rosen [*10*] have described the pathologic changes in the livers of rats following single and repeated toxic doses of urethane. They found an accumulation of transudate in perivascular and perisinusoidal spaces. The distended perisinusoidal spaces of Disse often contained erythrocytes and granular precipitates. Changes in the liver cells were minimal and were thought to be secondary to vascular injury. Similar hepatic changes in the guinea pig were described by Howe and Tedeschi [*11*]. Meacham et al. [*9*], as already indicated, reported the autopsy findings in a patient in whom hepatic insufficiency developed following the administration of urethane for one year. Death occurred two weeks after onset of the first symptoms of injury to the liver. Here again the lesions were primarily vascular and consisted of subintimal edema and necrosis of central veins and portal vessels.

The hepatic changes in our patient were consistent with late changes which might be expected three months following withdrawal of urethane. No acute effects were seen. The vascular necrosis and perisinusoidal edema found in acute urethane toxicity were absent, whereas many central veins and hepatic veins were obliterated by fibrosis and the spaces of Disse contained connective tissue, resulting in a diffuse perisinusoidal fibrosis. This pattern of fibrosis was probably a result of the organization of protein-rich exudate originally deposited during the phase of active vascular damage. This sequence of events has been proposed by Hill et al. [*12*] to explain the pattern of fibrosis following "serous hepatosis" in Jamaican children. The areas in which the parenchyma cells of the liver were narrowed and atrophic were in all probability caused by the fibrosis around the central veins and perisinusoidal spaces. The presence of plasma cells in the sinusoids and perisinusoidal spaces was associated with the multiple myeloma. Such infiltrations in the liver have been described in other cases of multiple myeloma but to our knowledge the unique type of fibrosis described in this paper has not been observed before in this disease [*13*] or in cases of viral hepatitis [*13,14*].

The essential feature in this case from a clinical standpoint was the sudden onset of marked ascites. The ascites was accompanied by only a slight degree of jaundice and there was no history of nausea or vomiting. The abrupt onset of ascites raised the question of possible thrombosis of the hepatic vein (Budd-Chiari syndrome). On the basis of liver function tests it is difficult to decide whether or not any significant liver cell necrosis was present initially. The slightly elevated serum bilirubin returned promptly to normal levels. Although the cephalin flocculation and thymol turbidity tests were abnormal, this conceivably could have been related more to the globulins of multiple myeloma rather than to any primary hepatic damage [*15*]. The prothrombin was noted to be low before urethane treatment and the onset of liver disease. There was no significant change in the abnormal electrophoretic pattern after the onset of liver disease. During the two episodes of hepatic coma there was again no definite laboratory evidence of cellular necrosis. The serum bilirubin, both direct and indirect, remained normal and there was no elevation in the serum transaminase. The only study that gave unequivocal evidence of liver disease was the bromsulphalein test, which was found to be elevated on two occasions. The second bromsulphalein test was obtained following the administration of four units of packed cells which corrected a severe anemia as well as a markedly increased plasma volume as determined by radioactive chromium (Cr^{51}) and I^{131} tagged human serum albumin. Pathologically, the liver showed little evidence of acute necrosis. The elevated bromsulphalein and the episodes of hepatic coma were most likely related to the partial isolation of the liver cells from the sinusoids and the central veins.

Although there are many factors in the causation of ascites in liver disease, it is believed that the sudden onset of ascites in this case was mainly due to mechanical obstruction. This could have been due initially to subintimal edema of the central veins, as described by Meacham et al. [*9*], and later to vascular fibrosis. In Meacham's patient [*9*] the onset of liver disease also was accompanied by the sudden onset of ascites, not associated with nausea, vomiting, jaundice or abdominal pain. The liver function tests were equivocal and did not show evidence of acute cellular necrosis. The bromsulphalein test revealed 13 per cent retention of dye in forty-five minutes.

Although it is possible that the administration

of urethane may produce different types of liver injury, it seems clear on the basis of animal experimentation, that in this patient, and the patient reported on by Meacham et al. [*9*] one of the primary effects of urethane is the production of vascular injury to the central veins, hepatic veins and sinusoids. Clinically this condition is most apt to manifest itself initially by an abrupt onset of ascites. The bromsulphalein test may well be the most sensitive liver function study for detecting this type of toxicity.

SUMMARY

A patient with chronic urethane toxicity of the liver is presented herein. The primary pathologic findings were a diffuse fibrosis involving the perisinusoidal spaces of Disse, central veins and hepatic veins. The outstanding clinical feature was the abrupt onset of abdominal ascites, associated only with bromsulphalein retention.

ADDENDUM

Since submission of this paper for publication, we have become aware of additional publications concerning the pathogenesis of hepatic fibrosis in Jamaican children. Serous hepatosis is now referred to as veno-occlusive disease of the liver [*16*]. Present evidence indicates that veno-occlusive disease is most likely caused by the ingestion of the pyrrolizidine group of alkaloids found in compositae (genus senecio), the leguminosae (genus crotalaria) and the boraginaceae (genus heliotropium) [*17*]. Extracts of the above plants frequently referred to as "bush teas" are commonly used in Jamaica for medicinal purposes [*16*]. It is of interest to note the marked similarity in pathologic disorders of the liver between the case described in this paper and cases of subacute and chronic veno-occlusive disease [*12,16*]. The acute subendothelial swelling of the hepatic veins in veno-occlusive disease is also quite similar to that described by Meacham et al. [*9*]. Veno-occlusive disease can be produced experimentally in rats by the injection of monocrotaline—a pyrrolizidine alkaloid [*17*]. It seems quite likely, therefore, that there may be a wide variety of toxic substances such as urethane and the pyrrolizidine alkaloids capable of producing hepatic disease by a direct vascular effect on the veins of the liver. Clinically the hallmark of such a condition would be the sudden onset of ascites.

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Cryptogenic Giant Cell Granuloma of Pituitary*

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Cryptogenic giant cell granuloma of the pituitary is an uncommon inflammatory condition which may be confined to the pituitary gland, or may also involve other organs. Microscopically, the affected tissues show numerous small granulomas. Some patients with the disease suffer from diminished pituitary function, usually of the anterior lobe, others may have no ill effects. Some have also had fever, muscle pains and eosinophilia.

The patient described in this study manifested clinical signs of hypopituitarism, hemolytic anemia and interstitial keratitis. At autopsy, granulomas were found in the pituitary, heart, kidney and adrenal, and trichinella larvae were found in the skeletal muscles.

Review of Literature

Cryptogenic giant cell granuloma of the pituitary was first described in 1917, by Simmonds [*1*], who presented five cases. In a review in 1952 Bleisch and Robbins [*2*] cited forty-six additional reports in the literature of granulomatous diseases of the pituitary and added five cases of their own. Seven additional cases have been reported since 1952 (Table 1), making a total of sixty-three case reports in the literature to date. How many of these represent "true" giant cell granuloma is difficult to assess, since well defined criteria for the diagnosis have not been set forth. The many similarities between this disease and sarcoidosis make classification of a given case difficult, even when the report is complete and the illustrations good. Bleisch and Robbins [*2*] and Russell [*3*] have commented on this problem. Our reasons for believing that giant cell granuloma is not a variant of sarcoidosis will be outlined in the discussion.

Sheehan and Summers [*4*] have described a condition believed by them to represent the end-stage of giant cell granuloma in which the pituitary gland may contract to a thin shell lying on the floor of the sella. A patient described by Rickards and Barrett [*5*] suffered from diminished pituitary function secondary to a disseminated granulomatous inflammation resembling sarcoidosis, even though the granulomas did not involve the pituitary parenchyma.

Case Report

A fifty-nine year old married woman was treated regularly as an outpatient for cholecystitis and cholelithiasis from 1954 to 1956. She refused surgical treatment. She was born in Italy, and came to California about 1930. She had been pregnant once; the pregnancy terminated in spontaneous abortion at three months. She had undergone the menopause in 1942 without incident. She did not use fava beans.

In 1957, after an absence from the clinic of over one year, she returned with symptoms referable to cholelithiasis, now much more severe, as well as lassitude, vague shifting muscle pains and weakness. Her weight had decreased from 142 to 124 pounds (64 to 56 kg.), and she appeared to have aged greatly. Her physician noted corneal opacities, which had not been present previously; these were interpreted by a consulting ophthalmologist as "healed interstitial keratitis." Her blood pressure was 145/90 mm. Hg, about the same as a year before. There was no abnormal pigmentation. A serologic test for syphilis was weakly reactive, and the Kahn reaction was 011. The serum protein-bound iodine level was 3.6 μg. per 100 ml. The patient improved slightly on therapy with desiccated thyroid and antispasmodics.

On January 1, 1958, she was hospitalized because of an exacerbation of her weakness, and mental confusion. Her blood pressure was 120/85 mm. Hg, and there was mild tenderness in the upper right quadrant of the abdomen. Shortly after admission she became comatose. Her temperature rose rapidly to 105°F. (40.6°C.). The serum sodium level was 130 mEq. per L., potassium 3.7 mEq. per L. There was quick response to therapy with intravenous sodium chloride solution, hydrocortisone and antibiotics. A few days later jaundice developed, and became very deep; it

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TABLE 1

CASES OF GIANT CELL PITUITARY GRANULOMA REPORTED SINCE 1952

Author	Age (yr.) and Sex	Clinical Data	Autopsy Findings
Russell [3]	...	Not given	Solitary pituitary granuloma (incidental finding)
Rickards and Barrett [5]	56,F	Hypotension, pigmentation, pretibial myxedema; low serum sodium	Non-caseating granuloma of pars intermedia of pituitary and adrenals; arteritis of one adrenal artery
Rickards and Harvey* Case 1	31,F	Anemia, muscle pain, ulcerative colitis	Pituitary enlarged, with numerous granulomas; ulcerative colitis, pancreatic fibrosis, high postmortem blood urea
Case 2*	54,F	Hypertensive cardiovascular disease with blindness; later hypotension, and erosion of clinoid processes	Tumor of tuber cinereum, with a few granulomas in hypothalamus, pituitary, and liver; atrophy of adrenals and thyroid
Sandison†	70,F	Coma	Pituitary granulomas
Klotz‡	49,M	Panhypopituitarism, proved by endocrine studies; long-standing tuberculosis and psychic disturbances; transitory hemiparesis; iridocyclitis; death with fever and diarrhea	Fibrosis of anterior pituitary, with no residual parenchymal cells; giant cell granulomas of meninges about pituitary stalk and of hypothalamus
Kucsko and Seitelberger§	25,F	Polyuria, amenorrhea, psychosis; xanthochromia and high protein level in spinal fluid	Infiltrating granuloma of diencephalon and neurohypophysis; lobar pneumonia; early cirrhosis.

* RICKARDS, A. G. and HARVEY, P. W. "Giant-cell granuloma" and other pituitary granulomata.

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§ KUCSKO, L. and SEITELBERGER, F. Das Granuloma infiltrans des Zwischenhirns und der Neurohypophyse. *Wiener Ztschr. Nervenh.*, 8: 187, 1954.

subsided in three weeks. Severe shifting muscle pains, especially in the right hip, were present during her hospital stay. She was discharged on January 31, 1958.

Other pertinent laboratory results during this admission included an icterus index of 11 on January 7, diminishing gradually thereafter. On January 4, at the height of the jaundice, the serum total bilirubin was 11.2 mg. per 100 ml., of which 10 mg. was indirect-reacting, and 1.2 mg. direct-reacting. Qualitative test for urinary urobilinogen gave a positive result only with undiluted urine. The urine did not contain bile.

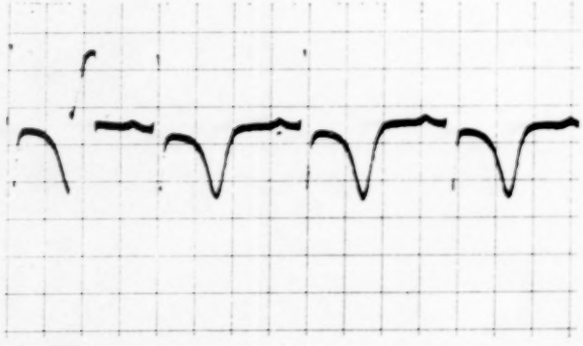

FIG. 1. Electrocardiogram, January 4, 1958, lead V_3, showing widened Q-T intervals, depressed S-T segments and inverted T wave.

The blood hemoglobin on admission was 13.1 gm. per 100 ml.; it fell to 12.4 gm. shortly after the onset of jaundice, and thereafter declined gradually to 10.9 gm. on discharge. The reticulocyte count was never above 1.4 per cent. Blood leukocytes varied from 4,000 to 5,000 per cu. mm., and repeated differential counts were within normal limits except for eosinophilia (12 per cent) on January 12. The results of the Kahn, Kolmer, direct and indirect Coombs', and Donath-Landsteiner tests were negative as was the serologic test for syphilis during her hospital stay.

An electrocardiogram on January 4 showed inverted T waves in all leads, with bizarre widening of the Q-T intervals and depressed S-T segments.

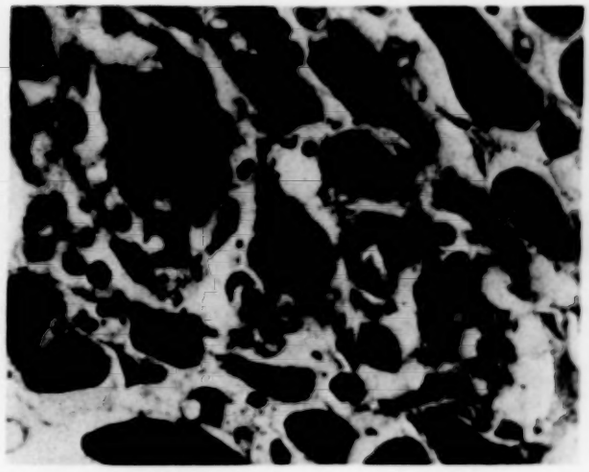

FIG. 2. Myocardial granuloma with two giant cells. The smaller contains a blue-staining inclusion of irregular shape. Hematoxylin and eosin stain, original magnification × 330.

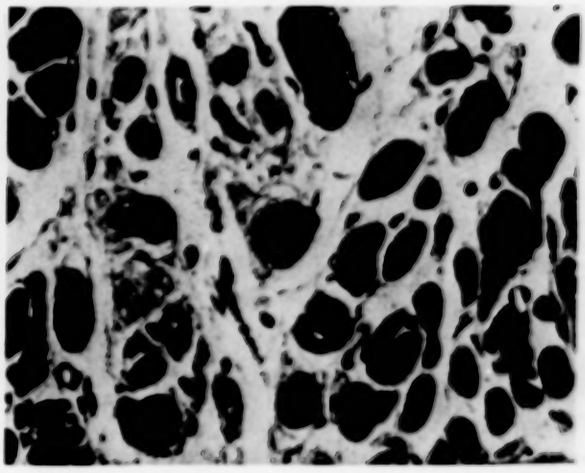

FIG. 3. Basophilic inclusion within myocardial fibers. Hematoxylin and eosin stain, original magnification × 330.

(Fig. 1.) On January 6, the Q-T abnormality was no longer present, but the inverted T waves persisted in most leads.

One month following discharge from the hospital, temperatures of 106°F. (41.2°C.) developed. She became irrational, and was noted to be slightly jaundiced. Her blood pressure was 100/60 mm. Hg. She was admitted to the hospital, and died a few hours later. The serum bilirubin was 3.9 mg. per 100 ml., of which 3 mg. was direct-reacting; other laboratory data were not significant.

Autopsy was performed twelve hours after death. The heart weighed 350 gm. The myocardium of the posterior wall of the left ventricle and of the septum showed ill-defined red discoloration. The spleen weighed 350 gm., and the red pulp was soft, with normally prominent white pulp markings. The lumen of the gallbladder was occupied by a hard stone 4 cm. long with alternating yellow and brown laminae on section. The cystic duct was very narrow. The hepatic and common ducts were dilated, the latter to a circumference of 2.5 cm., and their lumens contained thick, pale green bile. The ampulla was occluded by a stone 1.5 cm. in greatest length.

Grossly, the pituitary gland did not reveal any abnormalities. The thyroid gland weighed 20 gm. Its right lobe contained a poorly circumscribed, pale, fibrous area 2 cm. in diameter. The adrenals weighed 3 gm. each, and had thin bright yellow cortices. Muscle appeared normal. A uterine myoma, severe chronic cervicitis and mild generalized arteriosclerosis were also present.

On microscopic examination of the heart, numerous granulomas made up of monocytes and giant

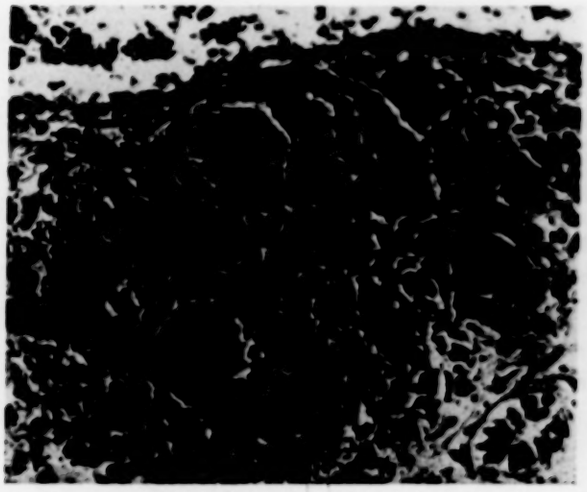

FIG. 4. Renal granuloma in wall of vein. Hematoxylin and eosin stain, original magnification × 330.

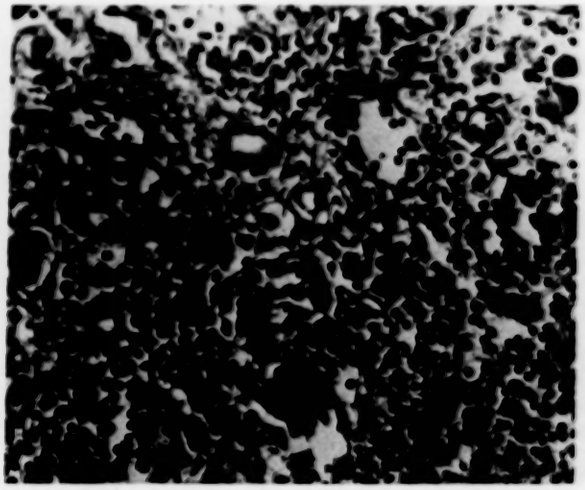

FIG. 5. Pituitary granuloma. Hematoxylin and eosin stain, original magnification × 330.

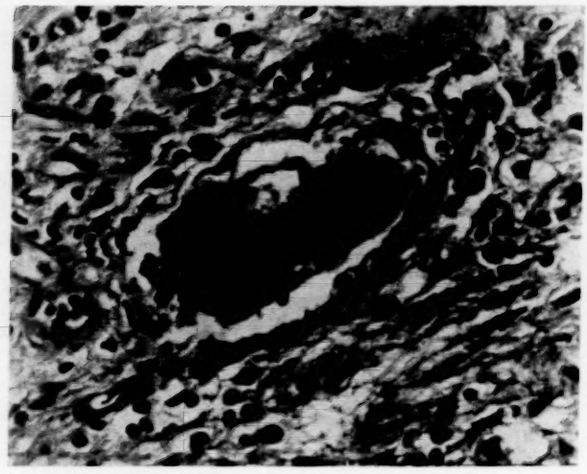

FIG. 6. Pituitary granuloma, showing refractile mass within giant cell. Hematoxylin and eosin stain, original magnification × 330.

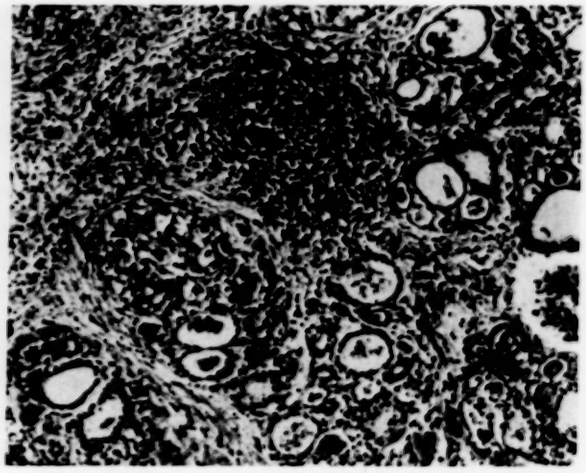

FIG. 7. Granulomatous thyroiditis. Hematoxylin and eosin stain, original magnification × 100.

cells (Fig. 2) were present. A few of the giant cells contained bits of material that stained brilliantly with the periodic acid-leukofuchsin (PAS) technic. A few PAS-positive basophilic bodies were noted within muscle fibers. (Fig. 3.) These are of unknown significance, and are possibly related to decreased thyroid function [*19*].

In the kidney a few granulomas were scattered throughout the renal capsule and peripelvic fat (Fig. 4); they contained no inclusions.

There was diffuse fibrosis of the anterior lobe of the pituitary, and the acini appeared atrophic, without visible lumens. The parenchymal cells were small, with small, round nuclei and scanty cytoplasm, resembling chromophobes. Numerous granulomas were present in the anterior lobe and a few in the capsule. (Fig. 5.) A few of the giant cells contained material that stained blue with hematoxylin and positively with von Kossa's stain, indicating calcification. These calcified masses were of irregular shape and size, and were not laminated. Other granulomas contained minute bits of refractile material, which did not stain with hematoxylin or PAS stains. (Fig. 6.) The posterior lobe appeared normal. The thyroid gland contained areas of fibrosis, acinar destruction, and infiltration with a few giant cells, without inclusions, resembling granulomatous thyroiditis. (Fig. 7.) The adrenal cortex was thin, with slight lipoid content in the fasicular and reticular zones. One small granuloma was present in the adrenal capsule.

No granulomas were noted in the spleen, lymph nodes, or marrow. Approximately 50 encysted Trichinella* larvae per cu. cm. of tissue were found in the skeletal muscle. (Fig. 8.) These were somewhat larger in diameter than usual, averaging 35 μ. Many were well preserved, inside a thick homogeneous cyst wall surrounded by plump mononuclear cells; others showed calcification and invasion by fibrous tissue. No eosinophils were seen in the inflammatory reaction surrounding the worms.

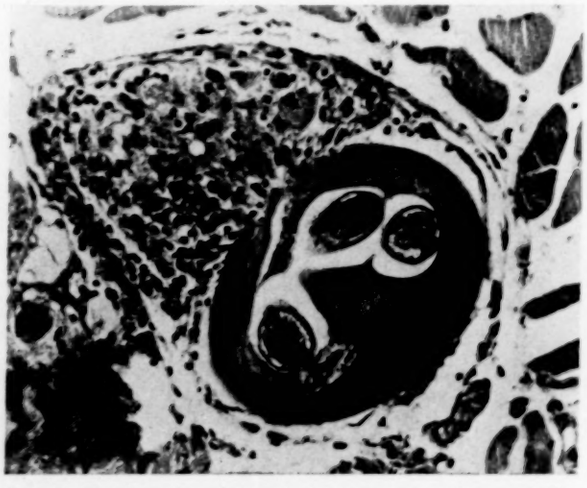

FIG. 8. Trichinella within skeletal muscle. Hematoxylin and eosin stain, original magnification × 100.

Interpretation of Findings. It is likely that the malaise, shifting muscle pains, weakness, weight loss, interstitial keratitis and positive reaction to the serologic test for syphilis that had their onset in 1957 represented the effects of disseminated giant cell granuloma. The larval infection is more difficult to date, but probably occurred at the same time. On admission to the hospital the patient had well developed signs of adrenal hypofunction. Soon she suffered a solitary episode of hemolytic anemia, manifested by a fall in blood hemoglobin level and transitory jaundice with high indirect-reacting fraction. However, the urinary urobilinogen level was low, as measured by the semi-

* I wish to thank Edward K. Markell, PH.D., M.D. and Benjamin G. Chitwood, PH.D. for identification of the larvae.

quantitative serial dilution technic, and there may have been biliary obstruction at that time. The terminal episode of jaundice was apparently due to the stone in the common duct, as there was now a high direct-reacting bilirubin level.

COMMENTS

All the cases of cryptogenic giant cell granuloma of the pituitary reported to date have been identified at autopsy. If a case could be diagnosed antemortem, laboratory studies might elucidate the cause of the condition.

Although rare, giant cell granuloma should be considered a diagnostic possibility in any case of hypopituitarism not secondary to tumor or to shock (Sheehan's syndrome). We list the etiologic possibilities suggested by this case, and present evidence for and against each.

Syphilis: Oelbaum and Wainwright [6] have reported a case of giant cell granuloma of the pituitary in a young man with signs of congenital syphilis. Our patient had interstitial keratitis and a positive reaction to the serologic test for syphilis. Yet it is doubtful that she had syphilis, for reaction to the serologic test was weak and transient, and the interstitial keratitis of congenital syphilis rarely has its onset beyond the age of forty [7].

Interstitial keratitis is by no means specific for syphilis, and even in that condition may be secondary to associated hypopituitarism [8]. Furthermore, interstitial keratitis is commonly associated with onchocerciasis, suggesting a possible relationship to this patient's helminth infection [9].

Sarcoidosis: The similarities between Boeck's sarcoidosis and giant cell granuloma are obvious, and the difficulties in differential diagnosis have been referred to. Nevertheless, there are important differences. Involvement of the pituitary and heart is rare in sarcoidosis [10], but common in giant cell granuloma. The granulomas in the two conditions differ in fine structure. Sarcoid granulomas have sharply outlined margins, and the giant cells within them contain Schaumann bodies and asteroids. The lesions of giant cell granuloma are poorly circumscribed, and contain small, irregular, poorly calcified bodies, or small refractile inclusions. Furthermore, there are differences in reticulum pattern [11].

Hypersensitivity and autoimmune states: Granulomas occur in conditions in which the known or suspected cause is hypersensitivity, such as asthma [12], the Arthus phenomenon [13], Wegener's granulomatosis and some of the collagen diseases (e.g., rheumatoid arthritis). Hemolytic anemia may be a feature of certain of the latter group of conditions, especially lupus erythematosus and thrombotic thrombocytopenic purpura.

Some authorities believe that Hashimoto's thyroiditis may be due to the presence of circulating autoantibodies against thyroid parenchyma [14]. An autoimmune mechanism should therefore be included in a listing of possible causes of giant cell granuloma of the pituitary.

Viral infection: A viral cause has been proposed for granulomatous thyroiditis [15], which was one of the manifestations of our case. The possibility bears investigation that the pituitary granulomas result from viral invasion.

Trichinosis: Trichinosis may have been the cause of the pituitary granulomas in this case, either directly by invasion of the gland, or indirectly by an immune or hypersensitivity mechanism. One case report of giant cell granuloma suggests a possible association with trichinosis (Case 2 of Bleisch and Robbins [2]). An Italian man of fifty-nine, a victim of chronic anemia, had an episode characterized by weakness, aching in the legs, trembling and unsteadiness, without fever. His blood repeatedly showed eosinophilia. The reaction to a precipitin test for trichinosis was positive, although skin test reactions were negative. Muscle biopsy failed to reveal worms. Two years later he died suddenly, and autopsy revealed granulomas of the pituitary. None were found in other organs, and the appearance of the muscle at autopsy is not recorded.

Involvement of the pituitary in helminthiasis appears to be unusual. Gould [16], in his extensive monograph on trichinosis, does not mention involvement of the gland. Visceral larva migrans also seems to spare the gland [17]. A case report of pituitary hypofunction possibly due to cysticercosis is on record [18].

Since the cuticle of nematodes stains well with the PAS technic, the PAS-negative reaction of the refractile material found within the pituitary granulomas argues against direct invasion by the worms. On the other hand, the PAS-positive staining reaction of the material within the myocardial granulomas is suggestive of such direct invasion. It is of interest in this regard that, although trichinella larvae are rarely found in the heart, myocarditis is common in trichinosis [16].

SUMMARY

A case of giant cell pituitary granuloma with involvement of the pituitary gland and other organs is presented. Clinically, the patient manifested hypopituitarism, interstitial keratitis, eosinophilia, hemolytic anemia and a positive reaction to the serologic test for syphilis. Trichinosis was discovered at autopsy.

The cause of the granulomatous reaction is uncertain, but possibilities include trichinosis, viral infection, hypersensitivity disease and autoimmunity. Syphilis and sarcoidosis appear less likely.

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Subject Index

Subject Index

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JANUARY TO JUNE
1961

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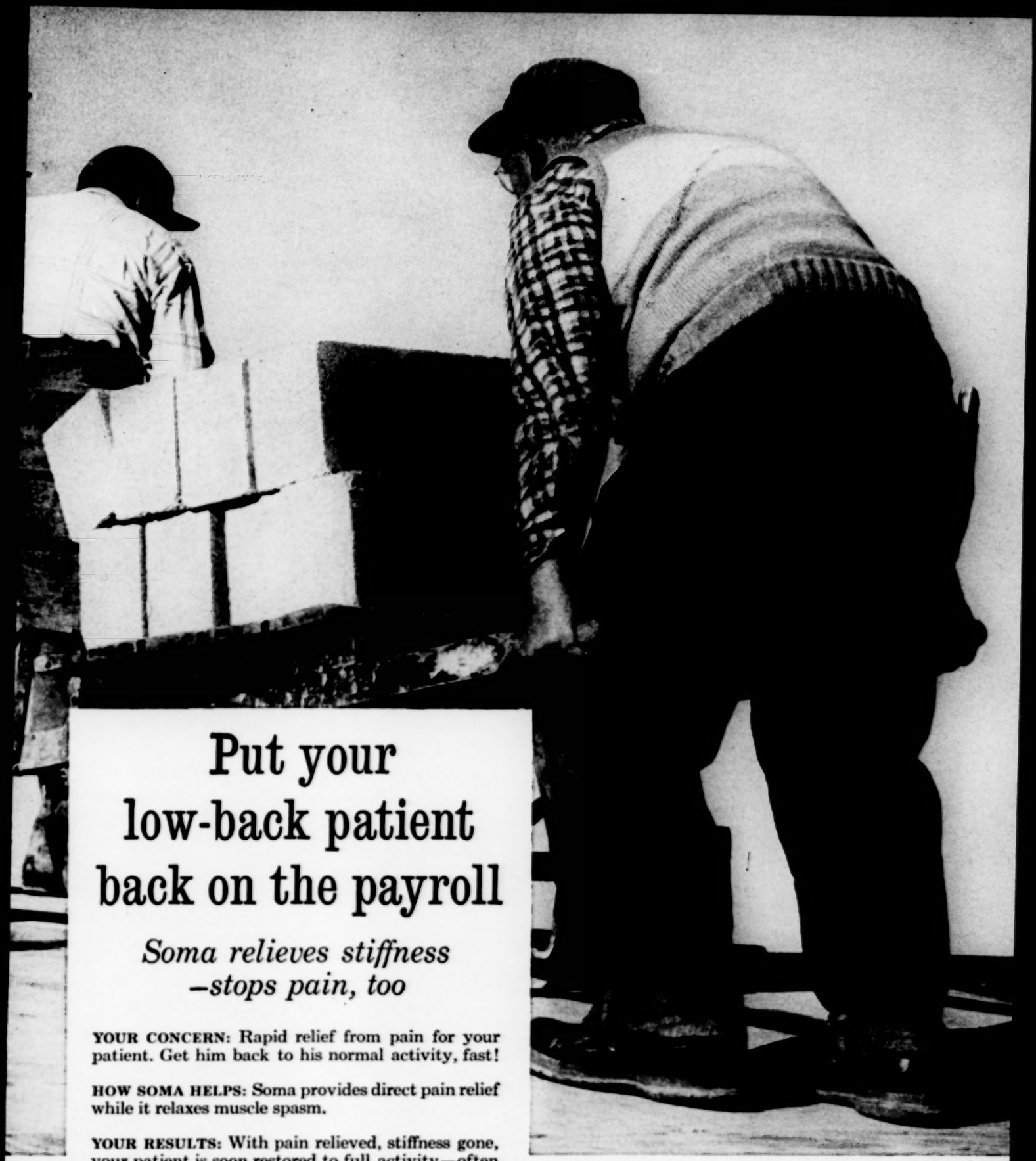

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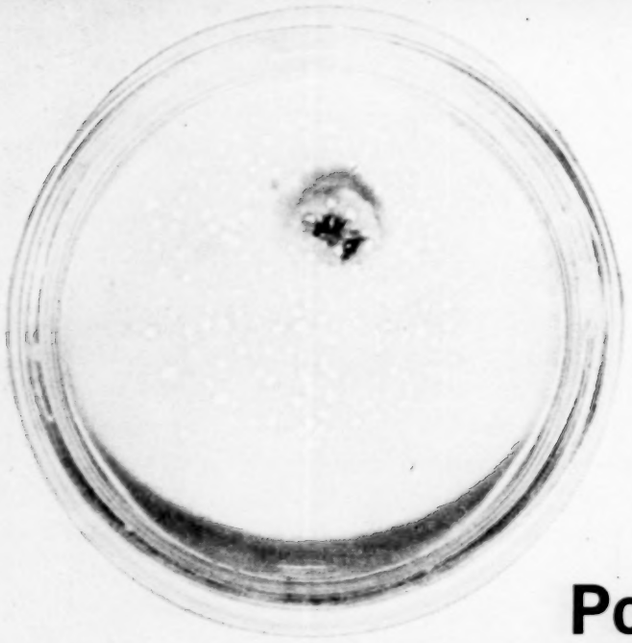

Potassium Penicillin V versus semi-synthetic penicillin

Recent clinical evidence sheds new light on some important questions...

Q. Which of the two oral penicillins provides greater antibacterial activity?
In a follow-up study[1] of oral penicillins, McCarthy and Finland compared the antibacterial activity of potassium penicillin V and semi-synthetic penicillin. They said: "Penicillin V provided greater activity than phenethicillin [semi-synthetic penicillin] against the streptococcus and pneumococcus, at least equivalent activity against the staphylococcus and sarcina in the serum and the same or greater activity in the urine . . ."

In another study[2], Griffith found that penicillin V not only produced peak levels of serum antibacterial activity faster, but produced values almost half again as high as those obtained with semi-synthetic penicillin.

A direct laboratory comparison[3] by Abbott scientists revealed a measurable difference in activity, milligram for milligram, between the two penicillins *in vitro*. Against four pathogenic strains (staphylococcus, streptococcus, pneumococcus, and corynebacterium species), potassium penicillin V exhibited from two to eight times the antibacterial activity of semi-synthetic penicillin.

Q. How valid are blood levels as a basis for comparison?
In comment on the two penicillins, McCarthy and Finland state[1]: "Thus, although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess . . . "

Q. Are there useful differences in resistance to penicillinase?
In another recent report[4], Geronimus commented: "Very large concentrations [of semi-synthetic penicillin] . . . were required to inhibit even so-called

moderately penicillin-resistant staphylococci when populations were employed that approached those found *in vivo*. Inferences regarding the possible effectiveness of phenethicillin in infections by penicillinase-producing staphylococci drawn by others from experiments with relatively minute inocula were found to be unwarranted."

McCarthy et al.[5] reached a similar conclusion: "Both of these penicillins [potassium penicillin V and phenethicillin] are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus*."

At Abbott, investigators studying the same subject[3] found that the rate of destruction of all three penicillins was so great that any differences were of no therapeutic significance.

Q. How does the safety of oral penicillins compare?

While surveys[6] have established that oral penicillin produces fewer and less severe reactions than does injectable penicillin, to date no clinical studies have produced any evidence that one oral form is less allergenic than another.

Q. What about recent editorials on oral penicillin?

Recently, New England Journal of Medicine editorialized[7]: "It thus appears that the major claims of phenethicillin over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-producing staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtue of importance that should impel one to choose over other available forms."

And in England, where semi-synthetic penicillin was first discovered and marketed, *British Medical Journal* editorialized[8]: "There is no evidence of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested."

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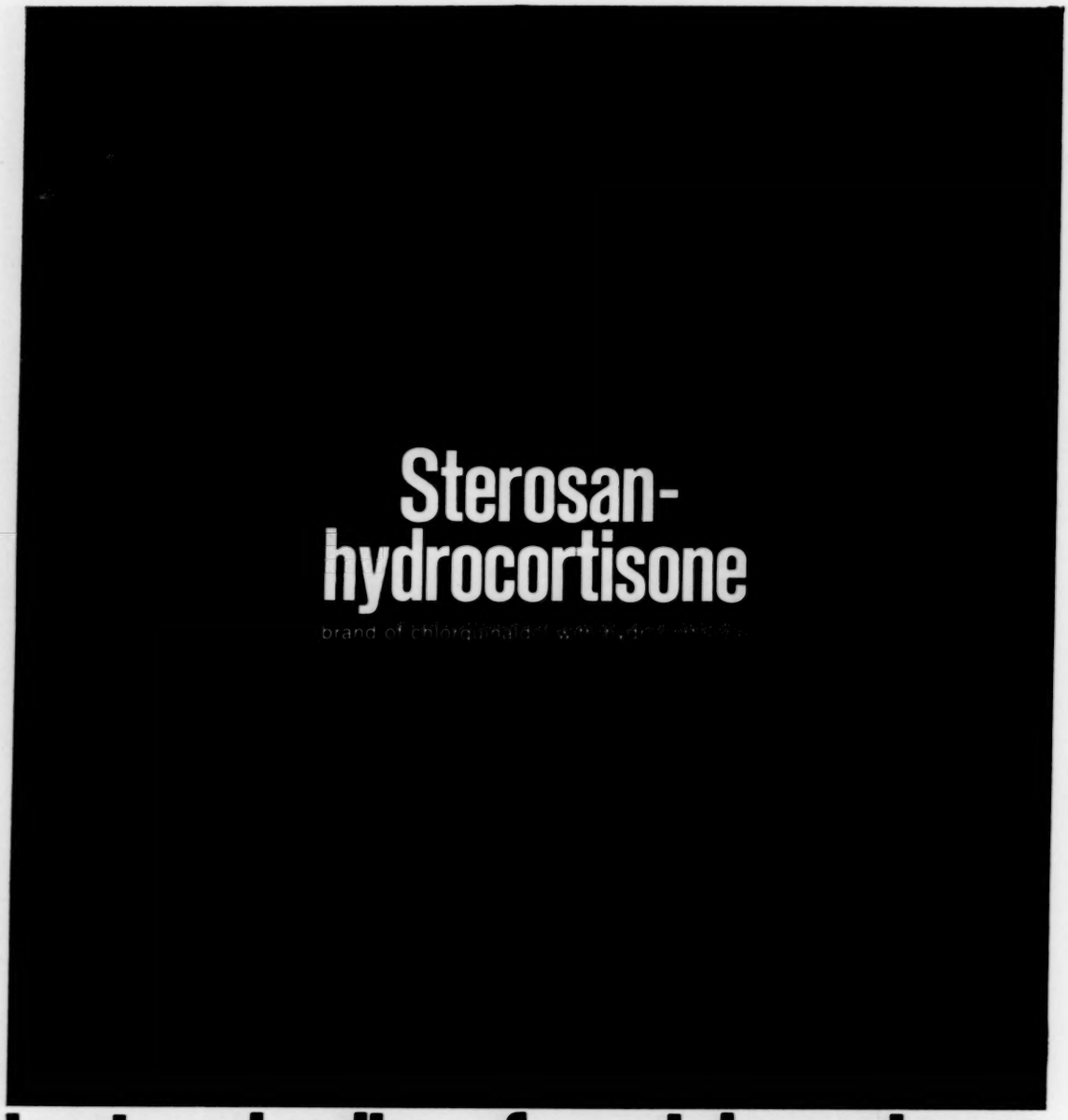

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References: (1) Lubowe, I. I.: Antibiot. Med. & Clin. Therap. **4**:81, 1957. (2) Fox, H. H.: Antibiot. Med. **6**:85, 1959. (3) Murphy, J. C.: Rocky Mountain M. J. **55**:53, 1958. (4) Pace, B. F.: Med. Rec. & Ann. **51**:370, 1957.

Sterosan®-hydrocortisone, brand of chlorquinaldol with hydrocortisone. Cream and Ointment containing 3% of Sterosan and 1% of hydrocortisone. Tubes of 5 and 20 Gm.

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RELIEVE ALL COMMON COLD SYMPTOMS AT ONCE

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THE TOTAL COLD-THERAPY TABLET

nasal decongestant · analgesic antipyretic · antihistamine

The ingredients combined in each 'Emprazil' tablet provide multiple drug action for prompt symptomatic relief of aches, pains, fever and respiratory congestion—due to common colds, flu or grippe—without gastric irritation.

Dosage: Adults and older children—One or two tablets t.i.d. as required. Children 6 to 12 years of age—One tablet t.i.d. as required.

Supplied: Bottles of 100 or 1000

Each orange and yellow layered tablet contains:

'Sudafed'® brand Pseudoephedrine Hydrochloride	20 mg.
'Perazil'® brand Chlorcyclizine Hydrochloride	15 mg.
Acetophenetidin	150 mg.
Aspirin (Acetylsalicylic Acid)	200 mg.
Caffeine	30 mg.

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Allergic or inflammatory flare-up!

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Rapid remission with new Celestone

the first major advance in corticosteroid therapy in over 2½ years

Clinical worth: CELESTONE provides greatly enhanced antiallergic and anti-inflammatory effects with significantly lower mg. dosages. Its efficacy and safety have been established by 20 months of pre-introductory clinical trials in such steroid-responsive disorders as:

- bronchial asthma
- pollenosis (severe hay fever)
- allergic/inflammatory dermatoses
- inflammatory eye diseases
- rheumatoid arthritis

Exceptional utility: From simple dermatoses to the more severe steroid-responsive conditions, the unexcelled anti-inflammatory effect of CELESTONE provides rapid clinical improvement with average daily dosages of from 2 to 8 tablets.

Ease of use: CELESTONE has simple-to-follow dosage schedules for all steroid-responsive disorders based on a single tablet strength, 0.6 mg. Patients may be switched easily from other corticosteroids to CELESTONE with proper dosage adjustments.

Safety-speed factor: CELESTONE is particularly valuable for short-term therapy of acute inflammatory episodes because inflammation is resolved quickly, thus helping to avoid certain corticoid side effects such as:

- weight loss
- anorexia
- vertigo
- severe headache
- sodium and water retention
- muscle weakness
- potassium excretion

Improved response: CELESTONE also offers the advantage of providing an opportunity to restore "lost" or diminished control in patients receiving other steroids.

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

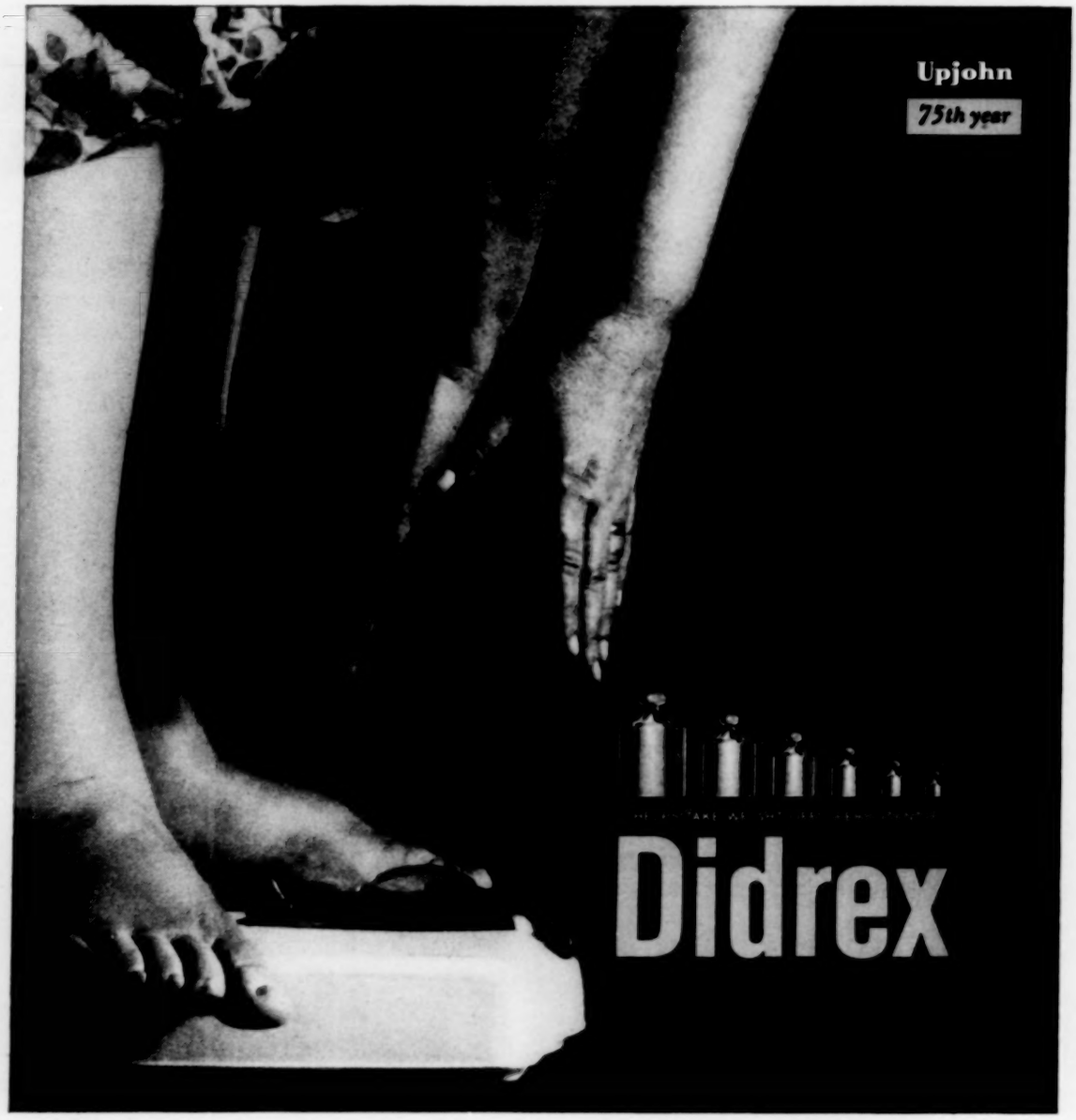
Bibliography: 1. Goldman, L.: Investigation of a New Steroid in Dermatology. Paper presented at First Symposium on the Clinical Application of Betamethasone: A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M. M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Gant, J. Q., and Gould, A. H.: Betamethasone: A Clinical Study. *Ibid.* 4. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.* 5. Hampton, S. F.: Betamethasone—A New Steroid in Allergy: A Preliminary Report. *Ibid.* 6. Bukantz, S. C.: Observations on the Use of Betamethasone in the Intractable Asthmatic Child. *Ibid.* 7. Bedell, H.: A New Systemic Steroid in the Treatment of Allergies in Office Practice. *Ibid.* 8. Schwartz, E.: Clinical Evaluation of Betamethasone in Chronic Intractable Bronchial Asthma. *Ibid.* 9. Kammerer, W. H.: Observations on the Effects of Betamethasone in Rheumatoid Arthritis. *Ibid.* 10. Cohen, A., and Goldman, J.: Management of Rheumatoid Arthritis with a New Steroid. *Ibid.* 11. Gordon, D. M.: Betamethasone—A New Corticosteroid in Ophthalmology. *Ibid.* 12. Abrahamson, I. A., Jr.: A Clinical Evaluation of Betamethasone. *Ibid.*

H-371

(betamethasone) **Tablets, 0.6 mg.**

CELESTONE™

a new magnitude in corticosteroid activity



Didrex doesn't perform miracles... it just helps the obese patient do it herself.

The reason is simple: persistent, significant loss of weight, up to 30 weeks in reported cases, helps to preclude the "weight plateau" that so often discourages dieters after a few weeks. Thus, time and will become your allies in changing the patient's dietary habits built over months or years of weight accumulation. Didrex may be used in closely supervised diabetic, coronary insufficient, and hypertensive patients.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N, α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of exogenous obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with ½ to 1 tablet (25 to 50 mg.) in mid-morning or mid-afternoon, according to the patient's eating habits for several days. Then "adjust" dosage to suit each patient's needs to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark—brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.

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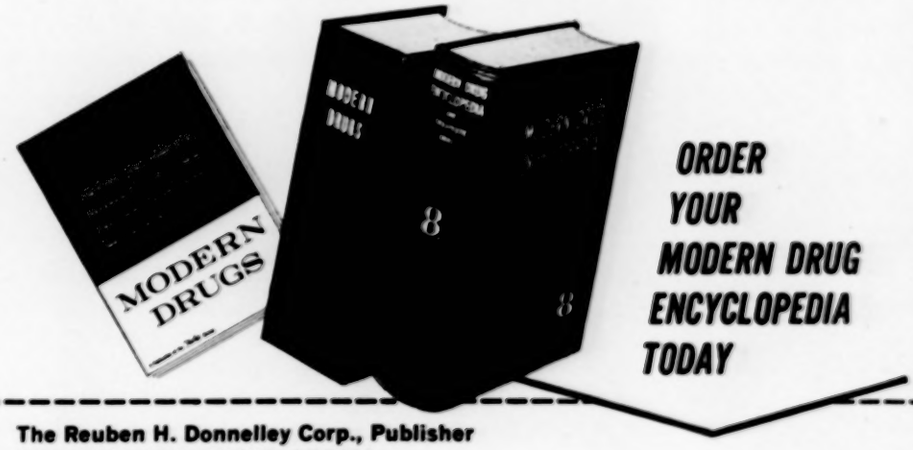

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provides remission of depression—smoothly, gradually, without "jarring" □ notably low incidence of serious complications or side effects □ convenience of once-a-day dosage

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restores
the will
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./***More detailed professional information available on request.***

Treating a respiratory allergy patient...with little response?

try NORISODRINE® syrup

(Isoproterenol Sulfate, Abbott)

with calcium iodide

You've seen the type. Racked by a chronic cough . . . or wheeze . . . or any of the other classic asthma symptoms. In any event, the usual treatment isn't affording adequate relief.

If you're faced with this kind of "problem" patient, try this: Put him on Norisodrine Syrup for two weeks—one or two teaspoonfuls, four to six times daily. See if this isn't evident:

Coughing will be more productive . . . and much less frequent. There will be a marked lessening of tension, physical and mental. Respiration will improve. Nighttime cough, particularly, will be relieved.

Good-tasting Norisodrine Syrup—a combination of Norisodrine (bronchodilator) and calcium iodide (expectorant)—can help you control symptoms in patients of all ages, even those who have been troubled for years.

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With proper medical management and adequate control of seizures, epileptic persons may lead productive, functioning lives.[1,2] To implement this goal, many clinicians rely on DILANTIN for outstanding control of grand mal and psychomotor attacks. "In most cases DILANTIN is the drug of choice.... Toxic symptoms are uncommon and when they do appear they are usually readily controlled; the drug is inexpensive, and widely available."[3] DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is available in several forms, including Kapseals, 0.03 Gm. and 0.1 Gm., bottles of 100 and 1,000.

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HELPS KEEP HIM IN THE MIDST OF THINGS

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Can a plumber do a day's work on 1200 calories?

The answer, of course, is "not for long." For example, following diagnosis of diabetes, a 44-year-old plumber (5'8" and weighing 147 lb.) had been put on a 1200-calorie diet to control glycosuria. When referred six months later, he had not been spilling sugar, but had lost 25 pounds and developed progressive fatigability. Orinase, 0.5 Gm./day, was prescribed and his diet was increased to 2800 calories to meet metabolic demands (125 Gm. protein; 300 Gm. carbohydrate; 125 Gm. fat).

Follow-up visits showed this progress:

3 mo. Urine and blood sugar o.k.; weight gain: 28 lb. Can work normally, feels generally well.

6 mo. Weight constant, control constant, no complaints.

12 mo. Same.

18 mo. Same.

24 mo. Same.

Diet-controlled diabetics who are underweight, tire easily, or have increased nutritional needs may merely be "getting by" on dietotherapy alone. These patients – and others who experience transient weakness or listlessness – can often be returned to near-normal activity by giving Orinase together with a more adequate diet. Orinase control of diabetes is notably smooth and stable; patients report a greater sense of well-being, an improved mood and outlook.

Case data courtesy Henry Dolger, M.D.

Indications and effects: The clinical indication for Orinase is stable diabetes mellitus. Its use brings about the lowering of blood sugar; glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear.

Dosage: There is no fixed regimen for initiating Orinase therapy. A simple and effective method is as follows: First day — 6 tablets; second day — 4 tablets; third day — 2 tablets. The daily dose is then adjusted — raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

In patients being converted from insulin, insulin is gradually withdrawn in accordance with the response to Orinase observed over a trial period that may extend to three or four weeks. In candidates for combined Orinase-insulin therapy, an individualized schedule is usually obtainable during a trial course of two or more weeks.

Contraindications and side effects: Orinase is contraindicated in patients having juvenile or growth-onset, unstable or brittle types of diabetes mellitus; history of diabetic coma, fever, severe trauma or gangrene.

Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythema, and urticarial, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 600,000 diabetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:
Tolbutamide ..... 0.5 Gm.
Supplied: In bottles of 50.

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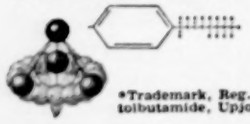
An exclusive methyl "governor" prevents hypoglycemia.



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dosage

Generally, the most effective dosage is 20 mg. t.i.d.

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real or potential
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anticholinergic . . .
treats the trauma

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Indications: duodenal ulcer; gastric ulcer; intestinal colic; spastic and irritable colon; ileitis; esophageal spasm; anxiety neurosis with gastrointestinal symptoms, and gastric hypermotility.

Administration and Dosage: PATHIBAMATE-400 (full meprobamate effect)—1 tablet three times a day at mealtime, and 2 tablets at bedtime. PATHIBAMATE-200 (limited meprobamate effect)—1 or 2 tablets three times a day at mealtime, and 2 tablets at bedtime. Adjust to patient response.

Contraindications: glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

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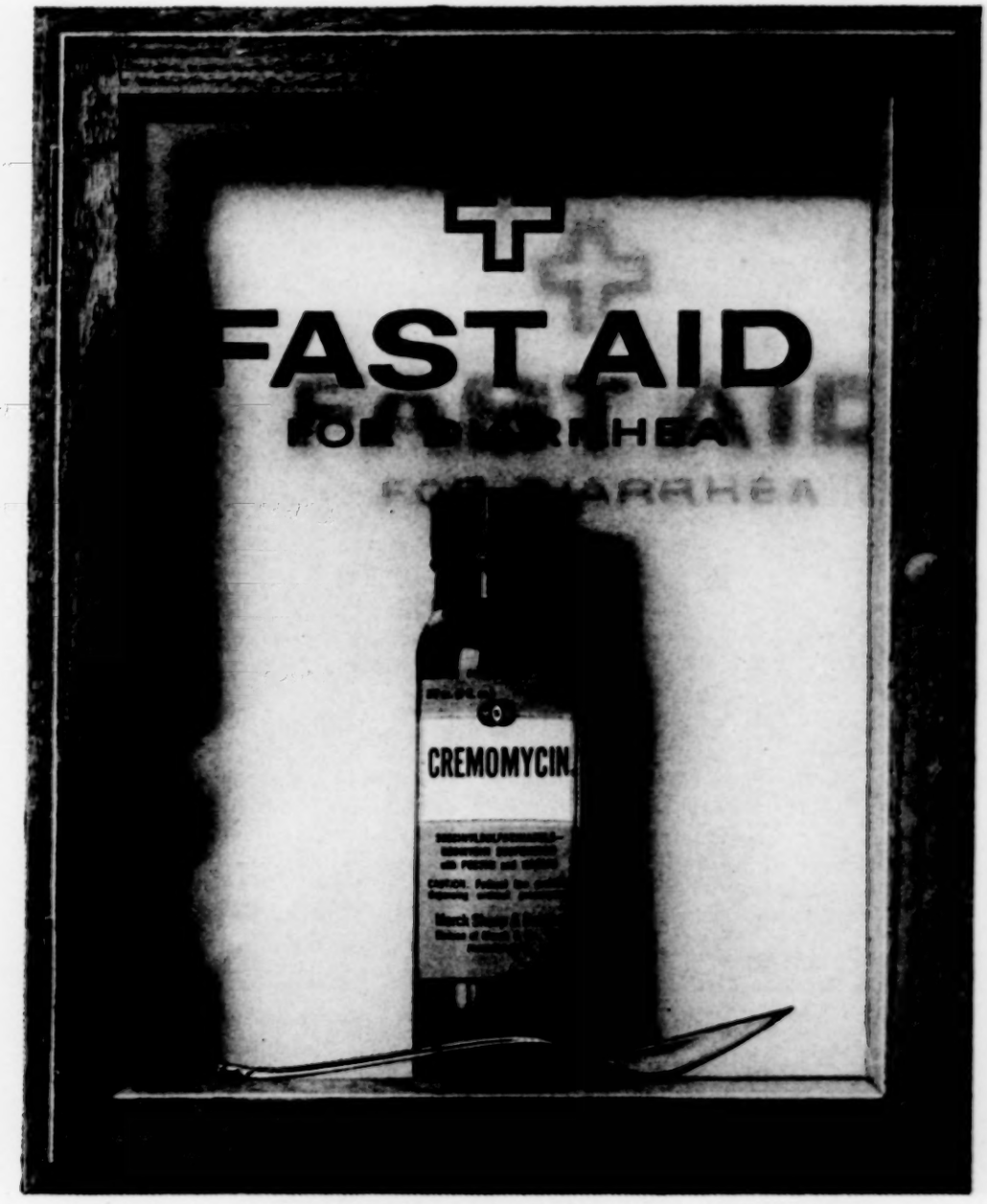

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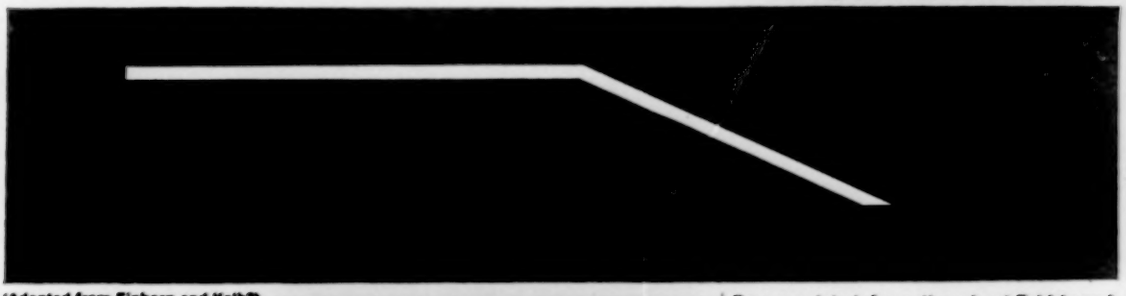
1. As an adjuvant in initiating treatment: Esidrix induces greater weight losses in the first few days than a conventional regimen.[1] This weight loss may be significant in itself (depending on the degree of fluid retention). But more than that, the quick loss of even a few pounds builds confidence in the weight-reducing program, inspires determination to follow it faithfully.

2. As an adjuvant in maintenance treatment: Esidrix eliminates retained water—with consequent weight losses—to break through the weight plateaus so often encountered in antiobesity programs. (See schematic graph below.) The new weight loss cheers the patient and helps overcome his tendency to eat too much.



(Adapted from Einhorn and Kalb[2])

Esidrix

For complete information about Esidrix and Esidrix-K (including dosage, side effects, and cautions), see Physicians' Desk Reference, or write CIBA, Summit, N. J.

References: 1. Ray, R. E.: To be published. 2. Einhorn, H. P., and Kalb, S. W.: Clin. Med. 7:1995 (Oct.) 1960.

Supplied: ESIDRIX Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored). ESIDRIX-K Tablets 25/500 (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. **NEW STRENGTH ESIDRIX-K NOW AVAILABLE:** ESIDRIX-K Tablets 50/1000 (white, coated), each containing 50 mg. Esidrix and 1000 mg. potassium chloride.

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SUMMIT • NEW JERSEY

Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the Fe^{59} isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

erythropoietin levels—new criteria in diagnosis of anemia – Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

can medication increase erythropoietin levels? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF, the therapeutic cobalt-iron hematinic.

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For a complete background file on erythropoietin, please write to the Medical Service Department of:

The 24-hour diuretic-antihypertensive

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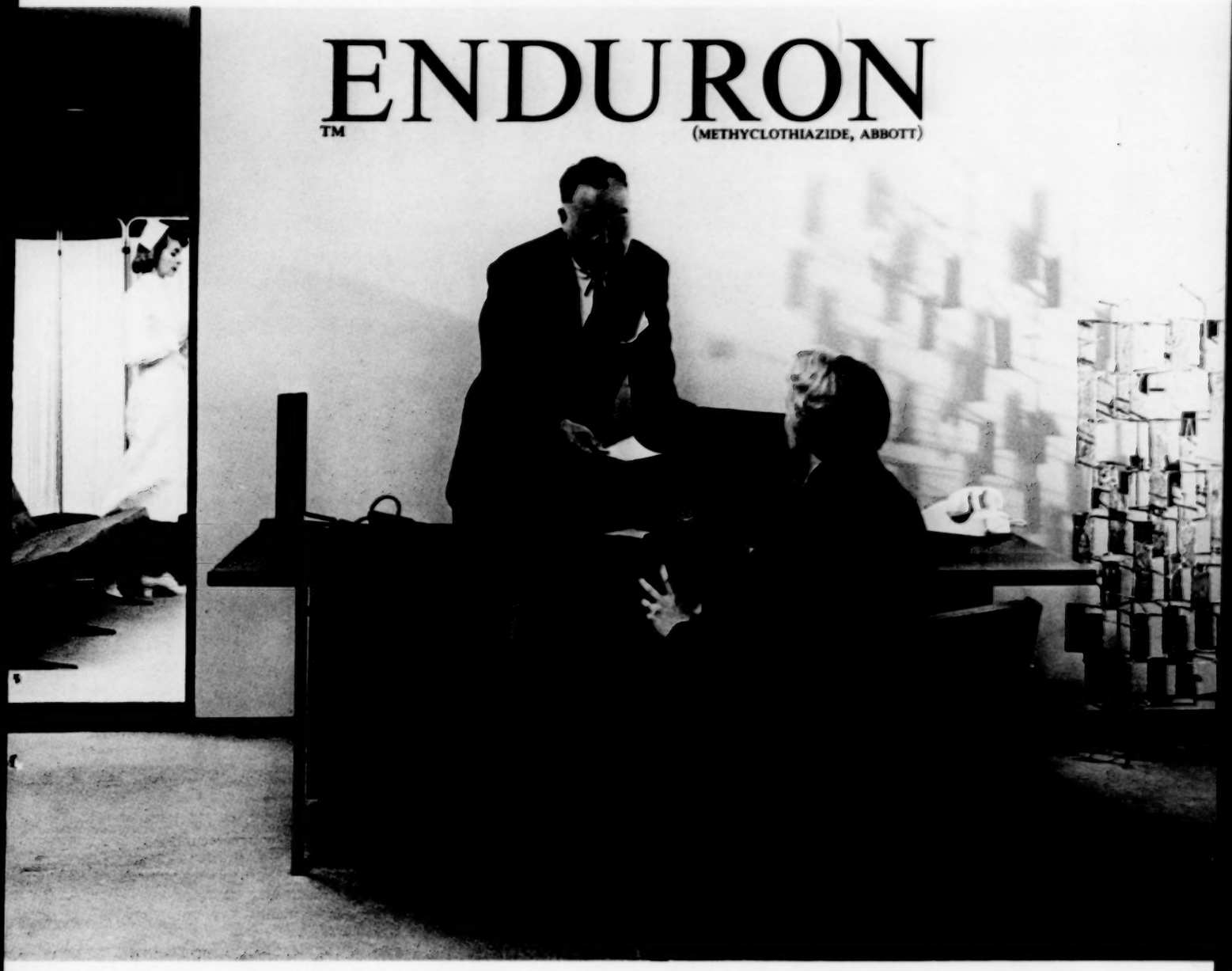


Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

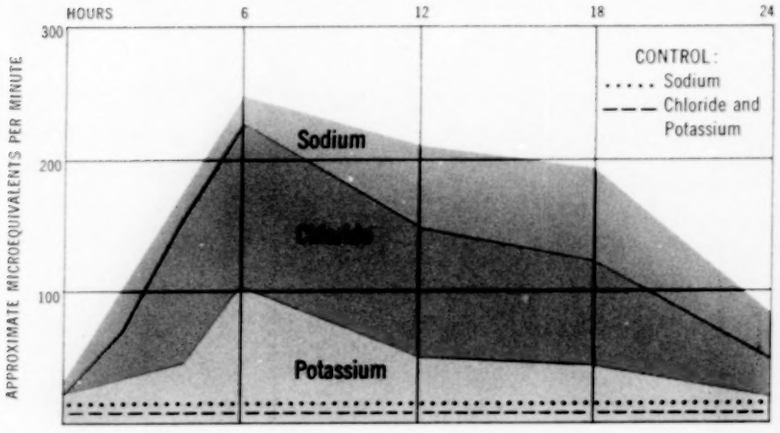
ABBOTT

1040.10A

Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

Usual Urinary Excretion Patterns Following 10 mg. of Enduron



Note that Enduron's effect on urinary potassium is minor; potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.[1]

How safe is Enduron?

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.

Prescribe the 24-hour diuretic-antihypertensive:

ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

ABBOTT

1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

1040108

suppress appetite ease emotional symptoms of food withdrawal

Ambar Extentabs®

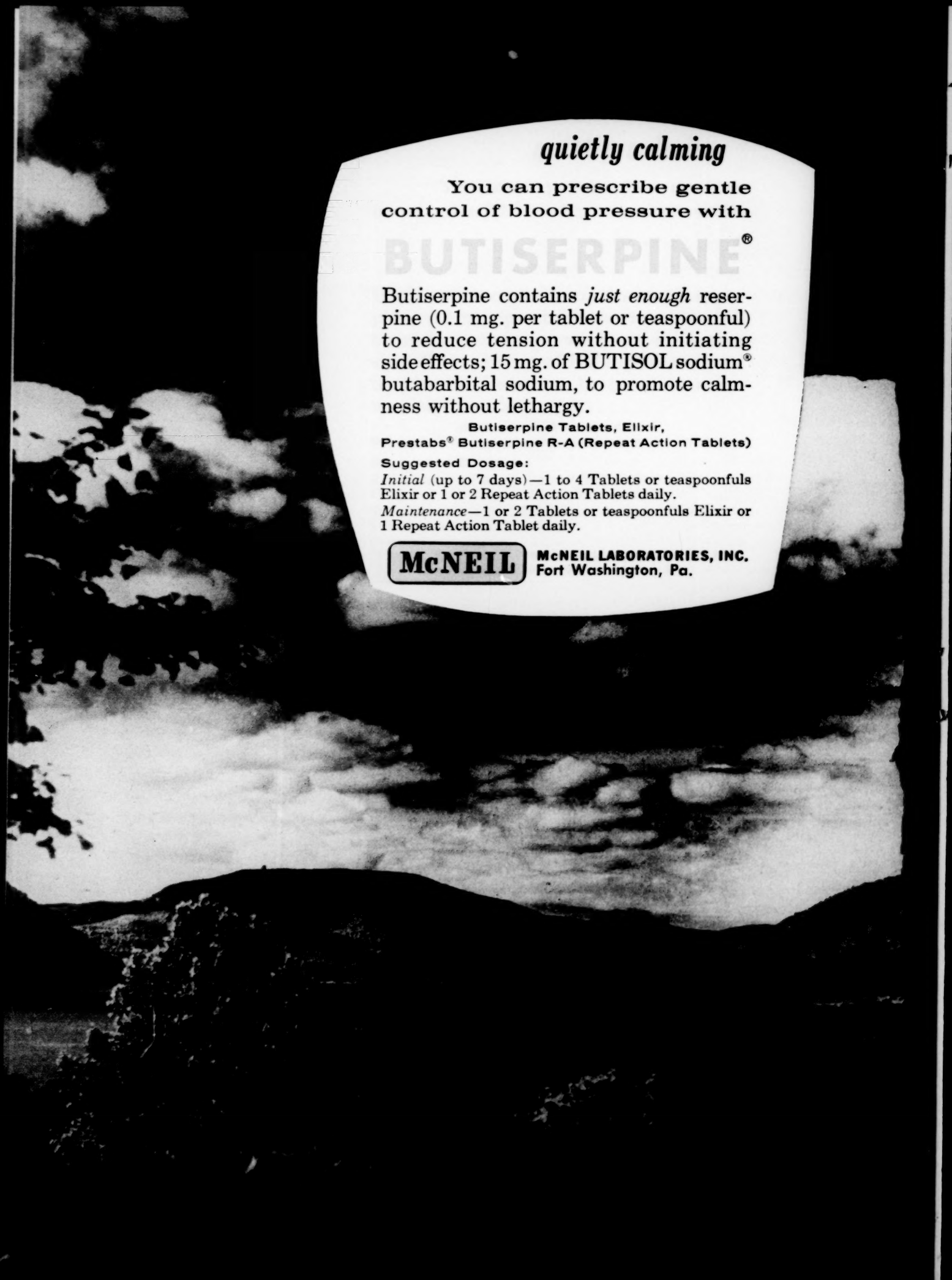
contain an optimal ratio of methamphetamine and phenobarbital to suppress appetite **and** ease emotional symptoms of food withdrawal. The improved mental outlook produced by Ambar provides the extra encouragement the patient needs to successfully complete a balanced over-all weight-reduction plan. Ambar Extentabs are available in two methamphetamine strengths to accommodate individual patient response to sympathomimetic amines and to meet the varying requirements of the overweight and the obesity prone.

Supplied: Each **Ambar #2 Extentab** contains: Methamphetamine HCl 15 mg., phenobarbital 64.8 mg. (1 gr.). Each **Ambar #1 Extentab** contains: Methamphetamine HCl 10.0 mg., phenobarbital 64.8 mg. (1 gr.). One Extentab® before breakfast provides appetite and mood control for 10 to 12 hours, in a single, controlled-release, extended action tablet.

Also available are regular **AMBAR TABLETS.** Each contains methamphetamine HCl 3.33 mg., phenobarbital 21.6 mg., (⅓ gr.). For use in conventional dosage schedules (one or two t.i.d.), or for intermittent or supplemental therapy.

Precautions: Administer Ambar with caution to patients with cardiovascular disease or hyperthyroidism. Contraindicated in those with idiosyncrasies toward barbiturates or sympathomimetics. Occasional side effects such as nervousness or excitement have been noted, but are usually infrequent and slight when Ambar's recommended dosages are followed.

A. H. ROBINS CO., INC., RICHMOND, VA.
MAKING TODAY'S MEDICINES WITH INTEGRITY
...SEEKING TOMORROW'S WITH PERSISTENCE



quietly calming

You can prescribe gentle control of blood pressure with

BUTISERPINE®

Butiserpine contains *just enough* reserpine (0.1 mg. per tablet or teaspoonful) to reduce tension without initiating side effects; 15 mg. of BUTISOL sodium® butabarbital sodium, to promote calmness without lethargy.

Butiserpine Tablets, Elixir,
Prestabs® Butiserpine R-A (Repeat Action Tablets)

Suggested Dosage:

Initial (up to 7 days)—1 to 4 Tablets or teaspoonfuls Elixir or 1 or 2 Repeat Action Tablets daily.

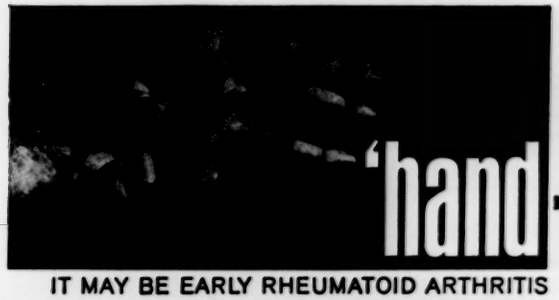
Maintenance—1 or 2 Tablets or teaspoonfuls Elixir or 1 Repeat Action Tablet daily.

McNEIL

McNEIL LABORATORIES, INC.
Fort Washington, Pa.

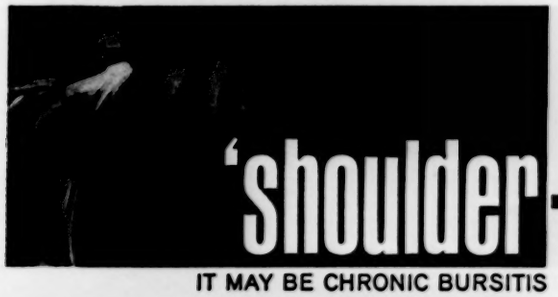
in any rheumatic 'itis'

Schering



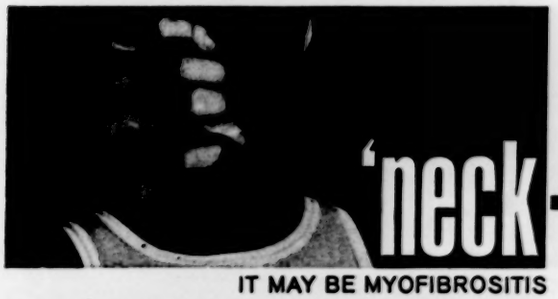
'hand-itis'

IT MAY BE EARLY RHEUMATOID ARTHRITIS



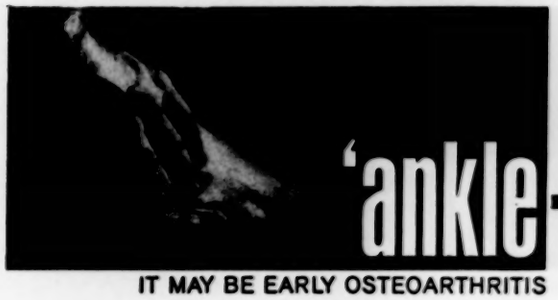
'shoulder-itis'

IT MAY BE CHRONIC BURSITIS



'neck-itis'

IT MAY BE MYOFIBROSITIS



'ankle-itis'

IT MAY BE EARLY OSTEOARTHRITIS

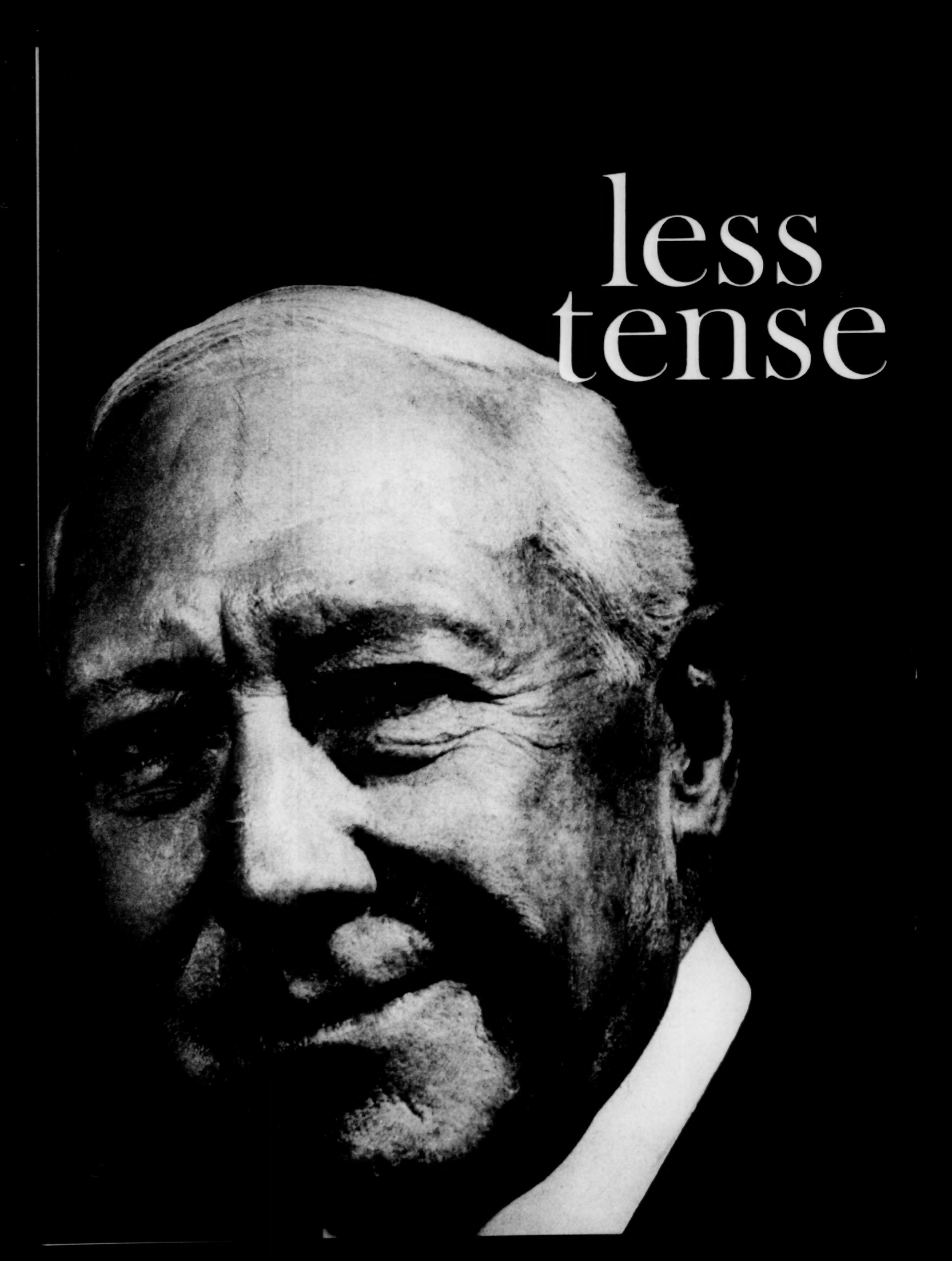
The favored corticoid-salicylate compound. For more effective and comprehensive, yet conservative, treatment than either steroids or salicylates alone... the outstanding anti-inflammatory effect of prednisone[1]...the supportive antirheumatic action of aspirin[2,3]...to bring rapid pain relief and quiet the inflammatory process. SIGMAGEN offers less likelihood of treatment-terminating side effects.[2] SIGMAGEN is available in bottles of 100 and 1000.

METICORTEN® (prednisone)	safer, reduced dosage	0.75 mg.
Acetylsalicylic acid	supportive anti-inflammatory-analgesic	325 mg.
Aluminum hydroxide	a buffer for better toleration	75 mg.
Ascorbic acid	anti-stress supplementation	20 mg.

References: 1. Cohen, A., et al.: J.A.M.A. 165:225, 1957. **2.** Spies, T. D., et al.: J.A.M.A. 159:645, 1955. **3.** Stecher, R. M.: Panel Discussion, Ohio M. J. 52:1037, 1956.

Remission-in any rheumatic 'itis' Sigmagen®

N-329


less
tense

BUTISOL SODIUM®
butabarbital sodium

"was found to be the most effective sedative which will produce satisfactory daytime sedation...with minimal occurrence of untoward reactions."[1]

...but still keen-eyed and alert

BUTISOL sodium®

butabarbital sodium

In a five-year study[2] of representative sedative and ataractic agents, BUTISOL SODIUM provided the highest therapeutic index (per cent of effectiveness: per cent of untoward reactions) for control of anxiety and insomnia by daytime dosage.

"The therapeutic index as defined in this study reflects clinical usefulness and indicates to what degree a sedative agent approaches the ideal."[2] It is significant that phenobarbital, although widely used in anxiety states, falls far short of the ideal.[2]

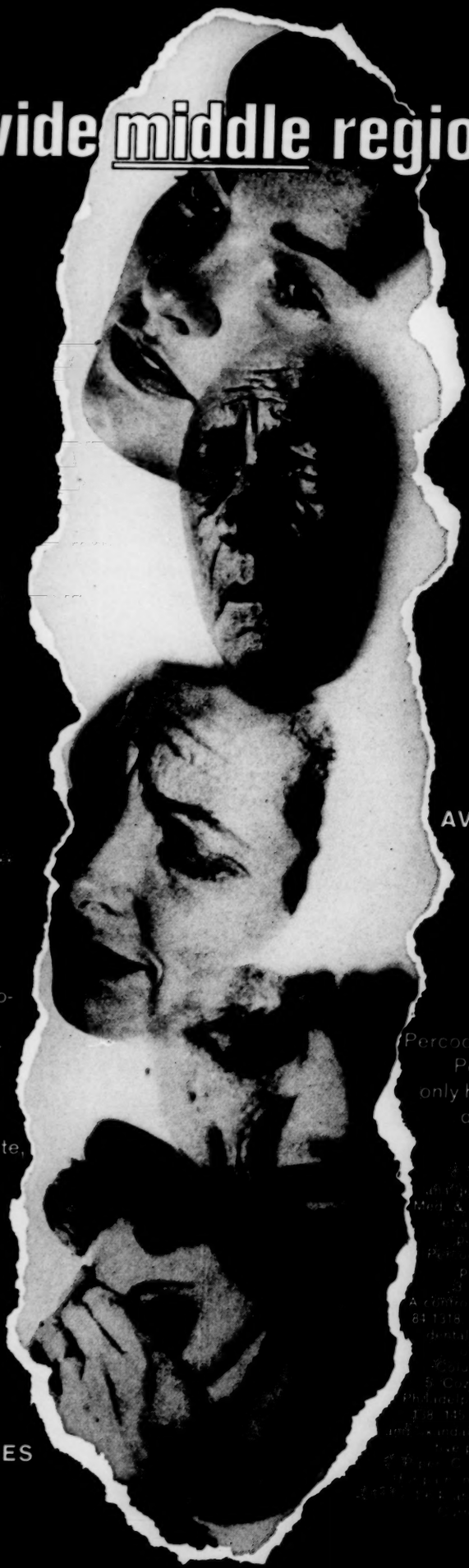
BUTISOL SODIUM® Tablets
Repeat-Action Tablets
Elixir/Capsules

McNEIL McNEIL LABORATORIES, INC., Fort Washington, Pa.

1. Grossman, A. J., Batterman, R. C., and Leifer, P.: Comparative Testing of Daytime Sedatives and Hypnotic Medications, Fed. Proc. *17*:373 (March) 1958.

2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. *26*:502-509 (October) 1959.

in the wide middle region of pain



Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

TABLETS

fills the gap between mild oral and potent parenteral analgesics[1-7]

- **acts in 5-15 minutes**
- **relief usually lasts 6 hours or longer**
- **toleration excellent... constipation rare**
- **sleep uninterrupted by pain**

Each Percodan* Tablet contains 4.50 mg. dihydrohydroxycodeinone HCl, 0.38 mg. dihydrohydroxycodeinone terephthalate (warning: may be habit-forming), 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

AVERAGE ADULT DOSE
1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

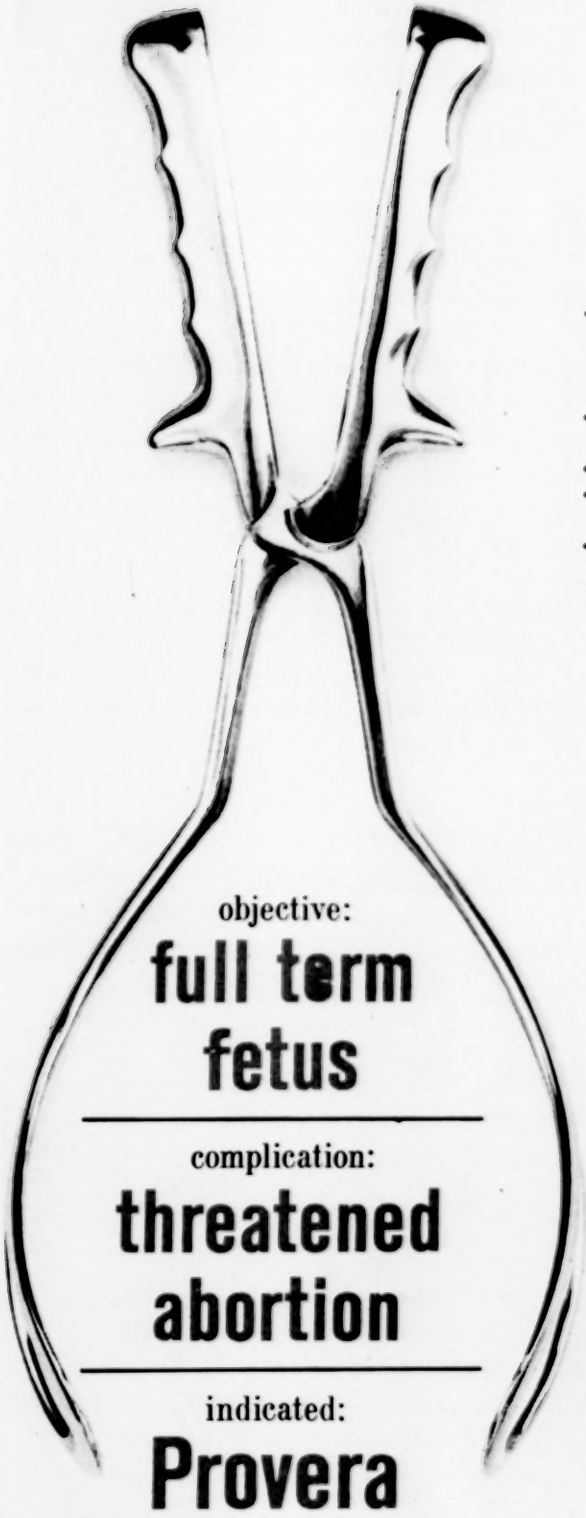
Also Available
For greater flexibility in dosage — Percodan®-Demi. The complete Percodan formula, but with only half the amount of salts of dihydrohydroxycodeinone and homatropine.

1. Beecher, H. K.: Measurement of Subjective Responses, New York, Oxford University Press, 1959.
2. Beecher, H. K.: Pain in Men Wounded in Battle, Ann. Surg. 123:96, 1946.
3. Beecher, H. K.: The Measurement of Pain, Pharmacol. Rev. 9:59, 1957.
4. Beecher, H. K.: Measurement of Pain in Relation to Dihydrohydroxycodeinone and Placebo, Evaluation of Medicines, New York, Josiah Macy, Jr. Foundation, 1955, p. 83.
5. Beecher, H. K.: Measurement of Pain in Relation to Dihydrohydroxycodeinone and Placebo, West. J. Surg. 65:84, 1957.
6. Cass, L. J., and Frederick, W. S.: A Controlled Study of Pain Relief, J. Pharmacol. & Exper. Therap. 118:116, 1956.
7. Chauncey, W. J.: Pain Relief in Dental Surgery, Postoperative Evaluation of the Pain-Free State, J. Dent. Res. 35:1, 1956.

Endo®

ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Pats. 2,628,185 and 2,907,768



objective:

full term fetus

complication:

threatened abortion

indicated:

Provera

Upjohn

Here are five reasons why:

- Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- It is four times as potent (by castrate assay) as any other progestational agent.
- No significant side effects have been encountered.
- It is available for both oral and parenteral administration
- Provera gives the economy of effective action from small doses.

Brief Basic Information

	Oral Provera*	I.M. Depo-Provera**
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

*TRADEMARK, REG. U. S. PAT. OFF. **TRADEMARK

Proven

in over six years of clinical use and
more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
2. no cumulative effects, thus no need for difficult dosage readjustments
3. does not produce ataxia, change in appetite or libido
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.
Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . . .

Meprospan®

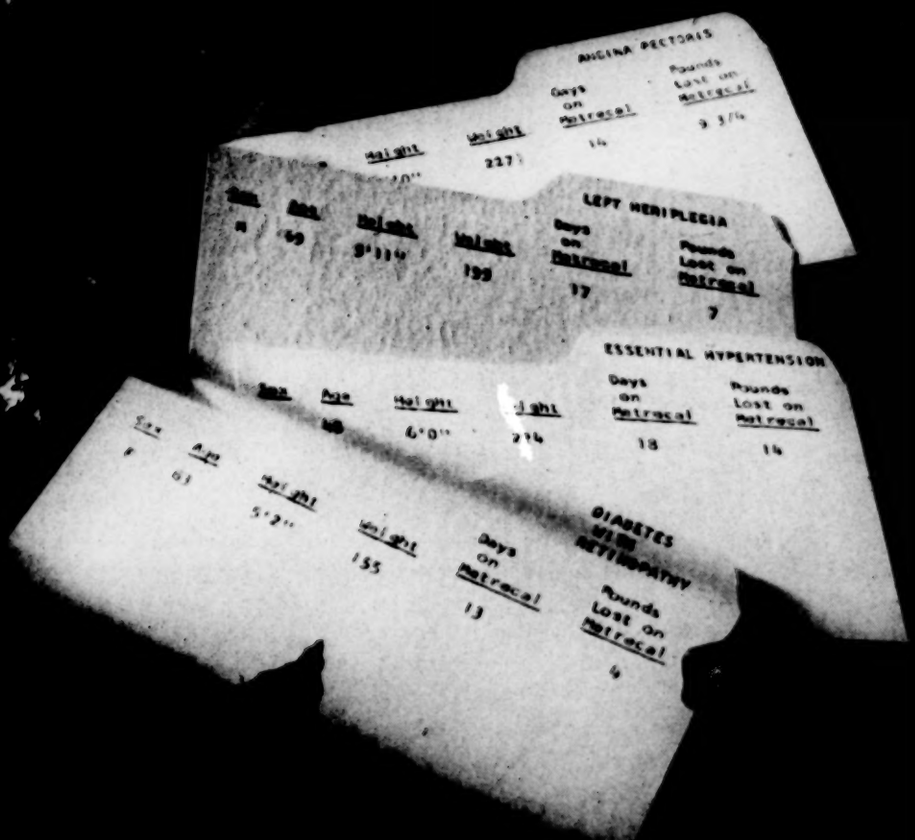
Available as Meprospan-400 (blue-topped *sustained-release* capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped *sustained-release* capsules containing 200 mg. meprobamate).

CM-4234

WALLACE LABORATORIES / *Cranbury, N. J.*

continued clinical evidence
...of safe and successful results
in weight-control studies with

Edward Dalton Co
MEAD JOHNSON & COMPANY



Advertisers' Product Index

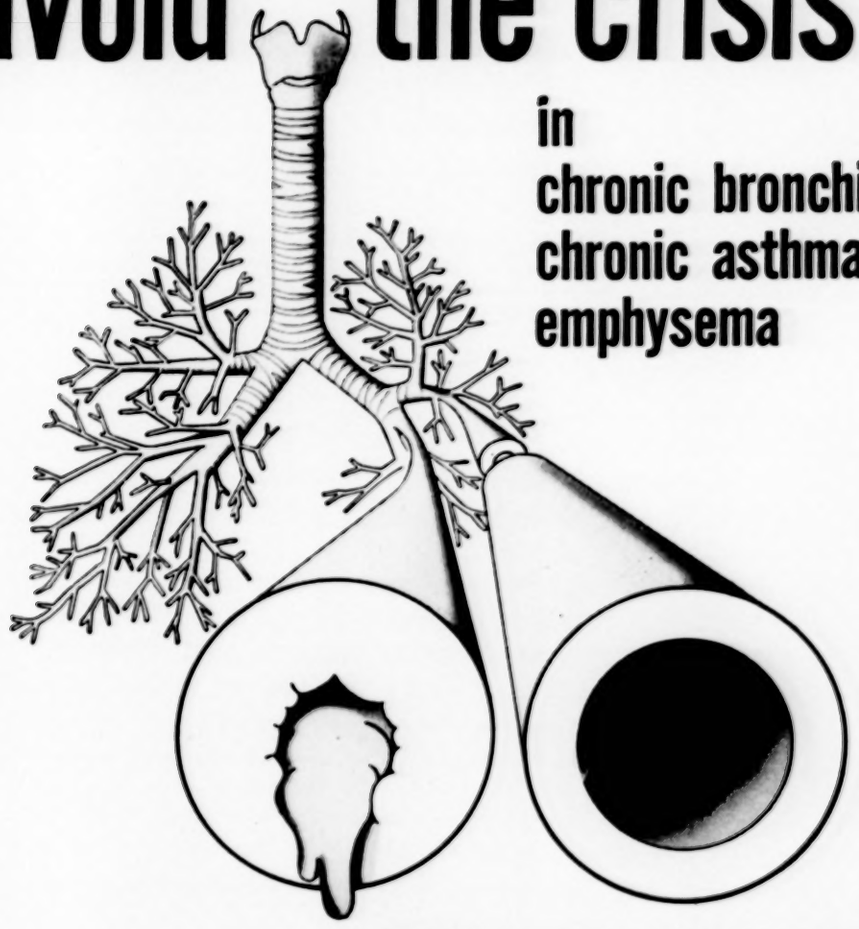
June, 1961

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA.**

*** Complete description of starred drugs will be found in MODERN DRUGS and THE MODERN DRUG ENCYCLOPEDIA.**

to avoid the crisis

in chronic bronchitis chronic asthma emphysema



Choledyl provides uniformly effective bronchodilatation throughout long-term therapy. Taken regularly, Choledyl helps prevent severe flare-ups in patients with chronic respiratory disease (the aging in particular) by affording continuous relief from debilitating bronchospasm. Gastric irritation and other unwanted effects are rare.

CHOLEDYL®

THE CHOLINE SALT OF THEOPHYLLINE

brand of oxtriphylline

keeps the airways open

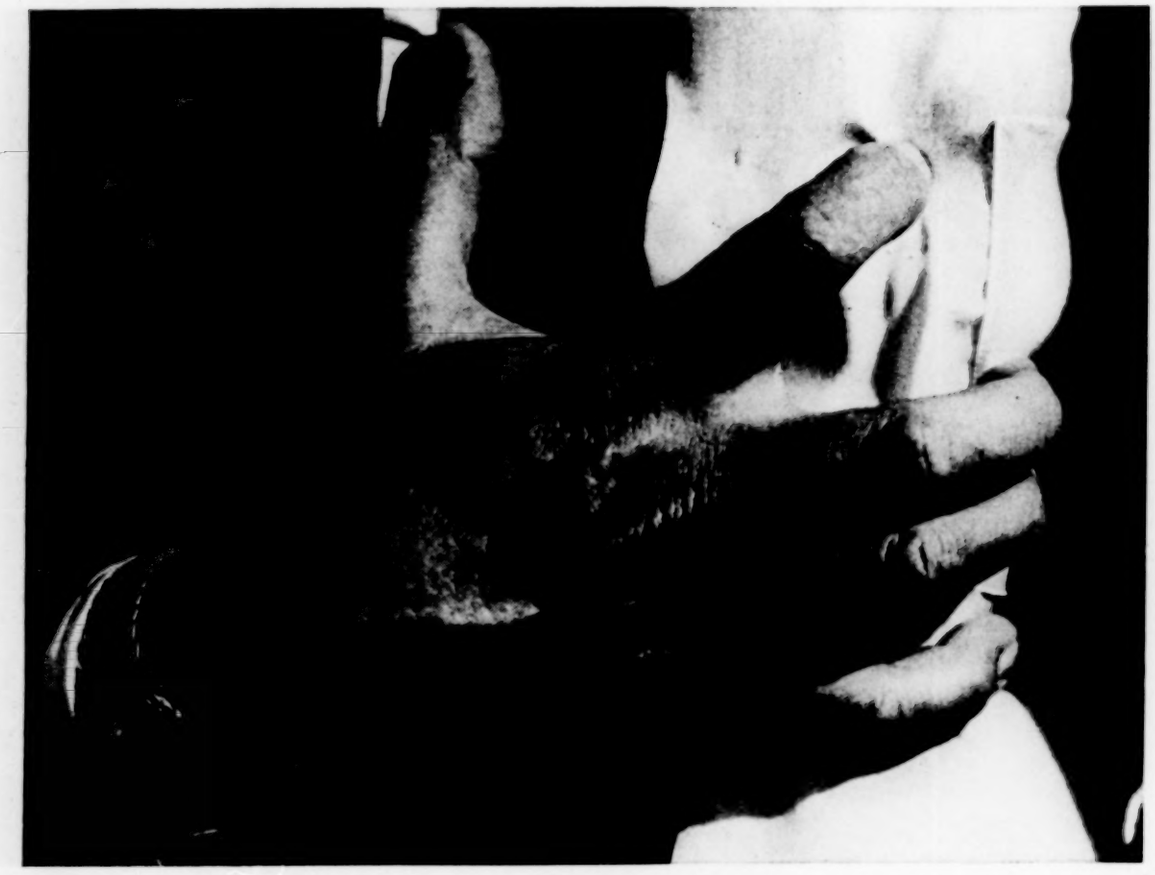
Supplied: 200 mg. tablets (yellow), bottles of 100. *Precautions:* Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. *Full dosage information, available on request, should be consulted before initiating therapy.*

WARNER CHILCOTT

MORRIS PLAINS, N.J.

makers of Tedral Gelusil Proloid Peritrate Mandelamine

GP12



Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.*: Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.*: Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

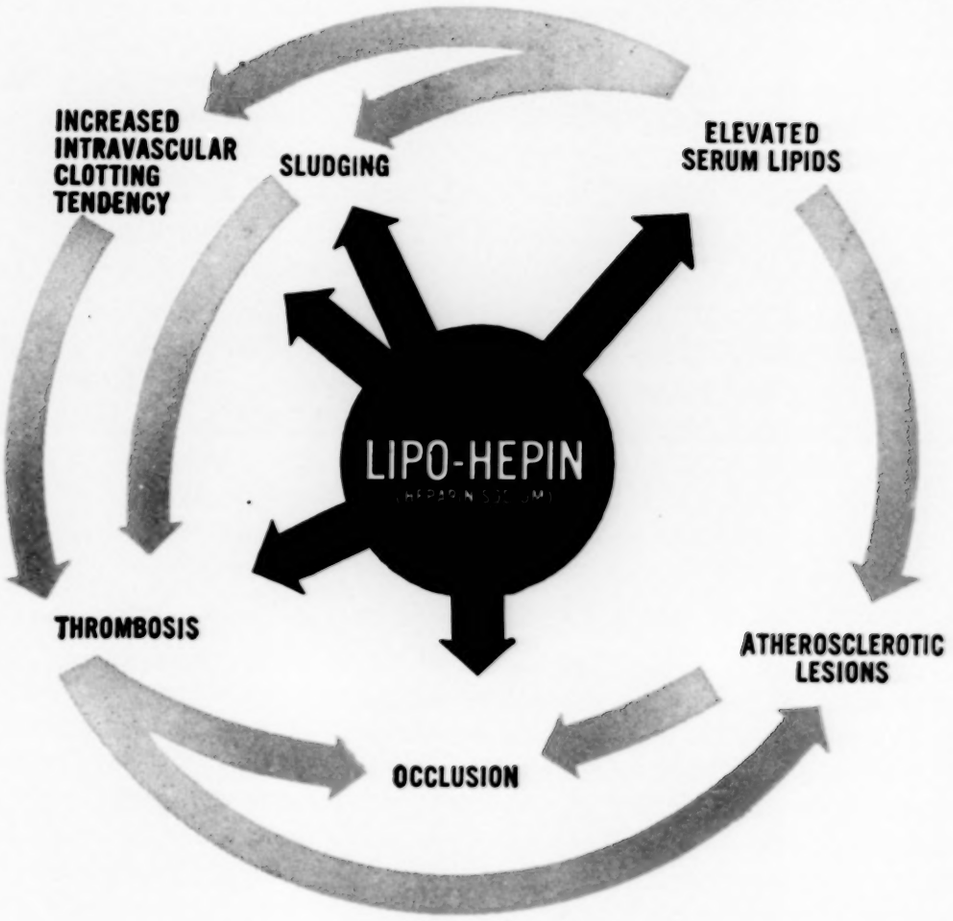
WALLACE LABORATORIES / *Cranbury, N. J.*

Positive Antithrombotic Therapy

HEPARIN

is the only substance that protects against the organization and extension of thrombi by acting on both the clotting mechanism and on elevated lipid levels.

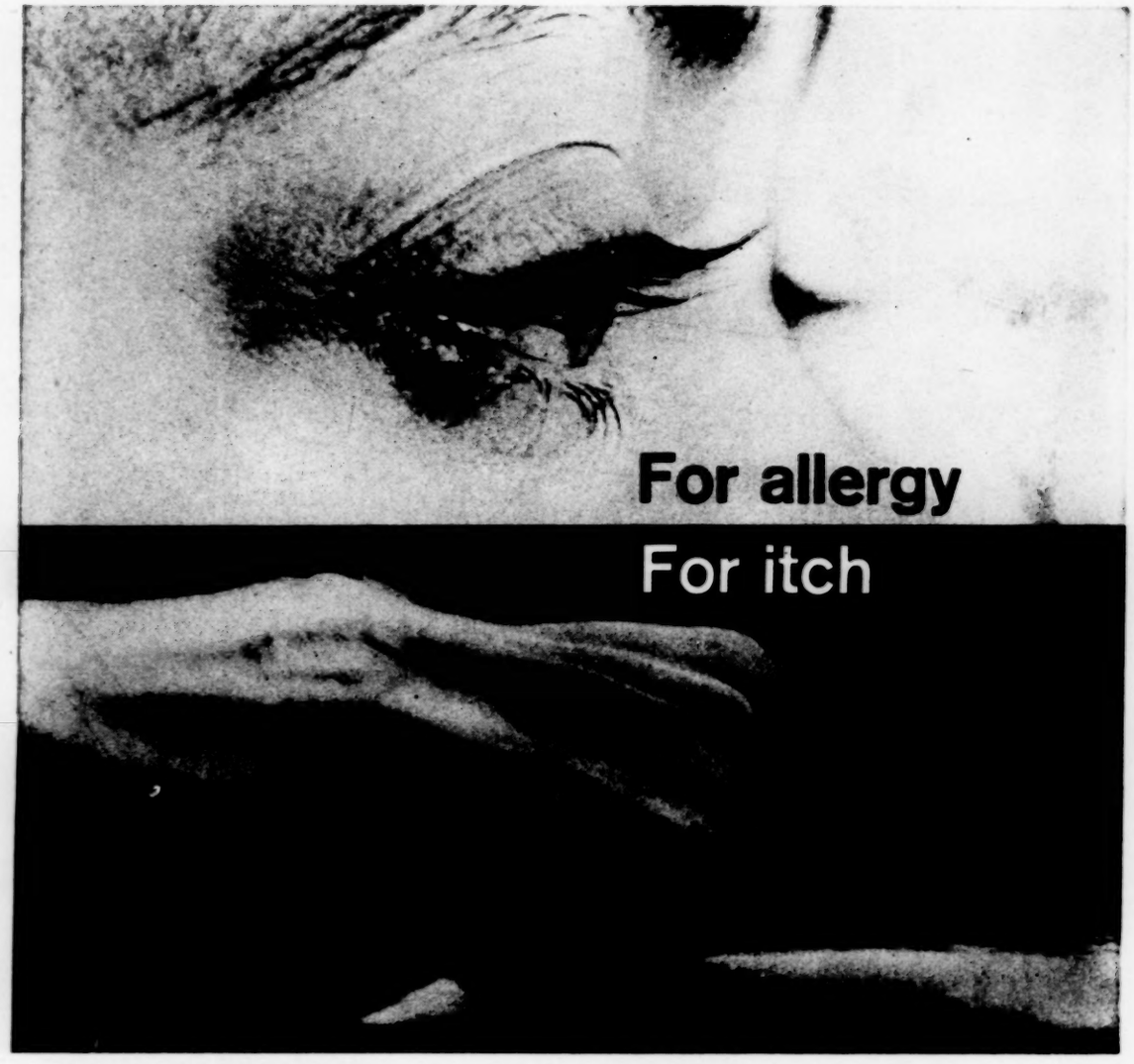
There is a growing body of evidence for inter-relationships among elevated serum lipids, atherosclerosis, hypercoagulability, and thrombosis.



LIPO-HEPIN

HEPARIN SODIUM INJECTION, AQUEOUS

RIKER LABORATORIES, INC.
NORTHRIDGE, CALIFORNIA



Everyday practice report:

Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 6181 cases have now been analyzed. In 3419 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

FORHISTAL® maleate (dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

new Forhistal® rated better than previous therapy in 7 cases out of 10

CIBA
SUMMIT, NEW JERSEY

2/2910MM-1